	Issue Date	Pages	Document ID	Title
1	20060525	27	US 20060111436 A1	Compositions and treatments for modulating kinase and/or HMG-CoA reductase
2	20060420	126	US 20060084695 A1	Compositions and treatments for inhibiting kinase and/or HMG-CoA reductase
3	20060216	91	US 20060035922 A1	Triazolopyridinylsulfanyl derivatives as p38 MAP kinase inhibitors
4	20051229	129	US 20050288306 A1	Compositions and treatments for inhibiting kinase and/or HMG-CoA reductase
5	20051222	125	US 20050282883 A1	Compositions and treatments for inhibiting kinase and/or HMG-CoA reductase
6	20051215	130	US 20050277653 A1	Compositions and treatments for inhibiting kinase and/or HMG-CoA reductase
7	20051208	127	US 20050272770 A1	Compositions and treatments for inhibiting kinase and/or HMG-CoA reductase
8	20051124	102	US 20050261836 A1	Crystal structure of mitogen-activated protein kinase-activated protein kinase 2 and binding pockets thereof
9	20051124	129	US 20050261354 A1	Compositions and treatments for inhibiting kinase and/or HMG-CoA reductase

	Issue Date	Pages	Document ID	Title
10	20051117	58	US 20050256122 A1	Substituted pyridazinones
11	20050915	126	US 20050203072 A1	Compositions, combinations, and methods for treating cardiovascular conditions and other associated conditions
12	20050811	447	US 20050176775 A1	Substituted pyridinones
13	20050630	51	US 20050143371 A1	Beta-carboline compounds and analogues thereof as mitogen-activated protein kinase-activated protein kinase-2 inhibitors
14	20050623	147	US 20050137220 A1	Beta-carboline compounds and analogues thereof as mitogen-activated protein kinase-activated protein kinase-2 inhibitors
15	20050512	63	US 20050101623 A1	Beta-carboline compounds and analogues thereof as mitogen-activated protein kinase-activated protein kinase-2 inhibitors
16	20050407	25	US 20050075352 A1	3,4-Dihydro-(1H)-quinazolin-2-ones and their use as CSBP/p38 kinase inhibitors
17	20050310	25	US 20050054591 A1	Yin yang-1

18	20050127	65	US 2005002059 4 A1	Substituted pyridazinones

	Issue Date	Pages	Document ID	Title
19	20041202	154	US 20040242608 A1	Substituted pyrimidinones
20	20040916	93	US 20040180038 A1	Effectors of innate immunity determination
21	20040909	636	US 20040176433 A1	Substituted pyrazoles as p38 kinase inhibitors
22	20040902	60	US 20040170995 A1	Isolated nucleic acid molecules encoding a novel human signal transducing kinase-mapkap-2; encoded proteins, cells transformed therewith and uses thereof
23	20040826	107	US 20040167197 A1	Compositions, combinations, and methods for treating cardiovascular conditions and other associated conditions
24	20040812	24	US 20040157877 A1	Cycloalkyl-[4-(trifluorophenyl)-oxazol-5yl]-triazolo-pyridines
25	20040729	29	US 20040147579 A1	3 (5) -heteroaryl substituted pyrazoles as p38 kinase inhibitors
26	20040722	35	US 20040143119 A1	Novel crystalline forms of 3-isopropyl-6-[4-(2,5-difluoro-phenyl)-oxazol-5- -yl]-[1,2,4]triazolo-[4,3-A]pyridine
27	20040722	57	US 20040142932 A1	Substituted pyridazinones

	Issue Date	Pages	Document ID	Title
28	20040701	410	US 20040127492 A1	Cyclic pyrazoles for the inhibition of mitogen activated protein kinase-activated protein kinase-2
29	20040513	31	US 20040092547 A1	Alkyl-[4-(difluorophenyl)-oxazol-5-yl]-triazolo-pyridines
30	20040506	24	US 20040087615 A1	Cycloalkyl-[4-(difluorophenyl)-oxazol-5-yl]-triazolo-pyridines
31	20040429	170	US 20040082551 A1	Novel pyrazoles and their use as p38 kinase inhibitors
32	20040422	25	US 20040077682 A1	Alkyl-[4-(trifluorophenyl)-oxazol-5-yl]-triazolo-pyridines
33	20040325	362	US 20040058964 A1	Substituted pyridinones
34	20040318	39	US 20040053958 A1	Di and trifluoro-triazolo-pyridines anti-inflammatory compounds
35	20040122	24	US 20040014973 A1	Pyridin-4-YL or pyrimidin-4-YL substituted pyrazines
36	20040101	85	US 20040001803 A1	Effectors of innate immunity determination
37	20031211	32	US 20030229110 A1	Novel substituted triazole compounds
38	20031204	66	US 20030225108 A1	Process for making substituted pyrazoles
39	20030814	25	US 20030153569 A1	Novel pyrazole and pyrazoline substituted compounds

40	20030731	34	US 2003014452 9 A1	Pyrazole derivatives as p38 kinase inhibitors

	Issue Date	Pages	Document ID	Title
41	20030731	51	US 20030144302 A1	Process for making substituted pyrazoles
42	20030619	33	US 20030114452 A1	Novel substituted imidazole compounds
43	20030605	49	US 20030104479 A1	Novel fusion proteins and assays for molecular binding
44	20030522	60	US 20030096838 A1	Novel triazolo-pyridines anti-inflammatory compounds
45	20030522	22	US 20030096243 A1	Methods and reagents for live-cell gene expression quantification
46	20030515	227	US 20030092749 A1	Novel benzimidazole anti-inflammatory compounds
47	20030424	54	US 20030078432 A1	Novel benzotriazoles anti-inflammatory compounds
48	20030410	34	US 20030069243 A1	Novel substituted imidazole compounds
49	20021226	33	US 20020198206 A1	Compounds of heteroaryl substituted imidazole, their pharmaceutical compositions and uses
50	20021024	24	US 20020156104 A1	NOVEL PYRAZOLE AND PYRAZOLINE SUBSTITUTED COMPOUNDS
51	20020704	28	US 20020086869 A1	3 (5) -heteroaryl substituted pyrazoles as p38 kinase inhibitors
52	20060704	536	US 7071198 B1	Substituted pyrazoles as p38 kinase inhibitors

53	20060627	312	US 7067540 B2	Substituted pyridinones

	Issue Date	Pages	Document ID	Title
54	20060606	48	US 7057049 B2	Process for making substituted pyrazoles
55	20060606	214	US 7056918 B2	Benzimidazole anti-inflammatory compounds
56	20060530	25	US 7053099 B1	3,4-dihydro-(1H)quinazolin-2-one compounds as CSBP/p38 kinase inhibitors
57	20060530	26	US 7053098 B1	3,4-Dihydro-(1H) quinazolin-2-one compounds as CSBP/P38 kinase inhibitors
58	20060502	23	US 7037923 B2	Alkyl-[4-(trifluorophenyl)-oxazol-5-yl]-triazolo-pyridines
59	20060328	22	US 7019005 B2	3 (5)-heteroaryl substituted pyrazoles as p38 kinase inhibitors
60	20060314	22	US 7012143 B2	Cycloalkyl-[4-(difluorophenyl)-oxazol-5-yl]-triazolo-pyridines
61	20060228	21	US 7005523 B2	Cycloalkyl-[4-(trifluorophenyl)-oxazol-5yl]-triazolo-pyridines
62	20060103	23	US 6982270 B1	3,4-dihydro-(1H)quinazolin-2-one compounds as CSBP/p38 kinase inhibitors
63	20051227	548	US 6979686 B1	Substituted pyrazoles as p38 kinase inhibitors
64	20050927	34	US 6949652 B2	Crystalline forms of 3-isopropyl-6-[4-(2,5-difluoro-phenyl)-oxazol-5-yl]-[1,2,4]triazolo-[4,3-A]pyridine

65	20050524	36	US 6897318 B2	Process for making substituted pyrazoles

	Issue Date	Pages	Document ID	Title
66	20050301	22	US 6861417 B2	Pyridin-4-YL or pyrimidin-4-YL substituted pyrazines
67	20050208	28	US 6852740 B2	Pyrazole derivatives as p38 kinase inhibitors
68	20040810	20	US 6774127 B2	Pyrazole and pyrazoline substituted compounds
69	20040706	27	US 6759410 B1	3,4-dihydro-(1H)-quinazolin-2-ones and their use as CSBP/p38 kinase inhibitors
70	20040504	28	US 6730683 B2	Compounds of heteroaryl substituted imidazole, their pharmaceutical compositions and uses
71	20040224	57	US 6696464 B2	Triazolo-pyridines anti-inflammatory compounds
72	20031216	50	US 6664395 B2	Benzotriazoles anti-inflammatory compounds
73	20030909	543	US 6617324 B1	Substituted pyrazoles as p38 kinase inhibitors
74	20030826	22	US 6610695 B1	Aryloxy substituted pyrimidine imidazole compounds
75	20030729	24	US 6599910 B1	Substituted triazole compounds
76	20030617	22	US 6579873 B2	3 (5)-heteroaryl substituted pyrazoles as p38 kinase inhibitors
77	20030527	32	US 6569871 B1	Substituted imidazole compounds
78	20030513	39	US 6562832 B1	Substituted imidazole compounds

	Issue Date	Pages	Document ID	Title
79	20030415	15	US 6548520 B1	Substituted imidazoles having anti-cancer and cytokine inhibitory activity
80	20030415	21	US 6548503 B1	Pyridin-4-yl or pyrimidin-4-yl substituted pyrazines
81	20030225	416	US 6525059 B1	Substituted pyrazoles as p38 kinase inhibitors
82	20030204	544	US 6514977 B1	Substituted pyrazoles as p38 kinase inhibitors
83	20030121	55	US 6509361 B1	1,5-Diaryl substituted pyrazoles as p38 kinase inhibitors
84	20030107	28	US 6503930 B1	Pyrazole derivatives as p38 kinase inhibitors
85	20021203	30	US 6489325 B1	Substituted imidazole compounds
86	20021022	20	US 6469018 B1	Compounds
87	20020723	584	US 6423713 B1	Substituted pyrazoles as p38 kinase inhibitors
88	20020326	18	US 6362193 B1	Cycloalkenyl substituted compounds
89	20020101	26	US 6335340 B1	compounds of heteroaryl substituted imidazole, their pharmaceutical compositons and uses
90	20020101	24	US 6335336 B1	3(5)-Heteroaryl substituted pyrazoles as p38 kinase inhibitors
91	20010626	35	US 6251914 B1	Cycloalkyl substituted imidazoles

	Issue Date	Pages	Document ID	Title
92	20010417	22	US 6218136 B1	Methods of the identification of pharmaceutically active compounds
93	20000711	24	US 6087496 A	Substituted pyrazoles suitable as p38 kinase inhibitors
94	20000711	31	US 6087381 A	Pyrazole derivatives as p38 kinase inhibitors
95	20000404	40	US 6046208 A	Substituted imidazole compounds
96	19990803	26	US 5932576 A	3(5)-heteroaryl substituted pyrazoles as p38 kinase inhibitors

	U	1	Issue Date	Pages	Document ID	Title	Current OR	Current XRef	Retrieval Classif
1			20040902	60	US 20040170995 A1	Isolated nucleic acid molecules encoding a novel human signal transducing kinase-mapkap-2; encoded proteins, cells transformed therewith and uses thereof	435/6	435/194; 435/320.1; 435/325; 435/69.1; 536/23.2	

	Inventor	S	C	P	2	3	4	5	Image Doc. Displayed	PT
1	Lograsso, Phillip et al.	X							US 20040170995	

	L #	Hits	Search Text
1	L1	4452	mitogen adj activated adj3 kinase$2
2	L2	96	MAPKAP-2
3	L3	4455	l1 or l2
4	L4	863908	clon$3 or express$3 or recombinant
5	L5	1580	l3 same l4
6	L6	1560	human and l5
7	L7	1630416	modulat$3 or inhibit$3 or activat$3
8	L8	1560	l6 and l7
9	L9	96	l2 and l7
10	L10	16287	LOGRASSO HAWKINS LISNOCK
11	L11	1	l2 and l10

10/469221

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=> d his

     (FILE 'HOME' ENTERED AT 16:11:16 ON 13 JUL 2006)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 16:11:42 ON 13 JUL 2006
L1        149956 S MITOGEN (W)ACTIVATED (3W) KINASE##
L2            37 S MAPKAP-2
L3        149966 S L1 OR L2
L4       7784549 S CLON? OR EXPRESS? OR RECOMBINANT
L5         85357 S L3 AND L4
L6         41653 S HUMAN AND L5
L7             5 S L2 (W)KINASE?
L8             4 DUP REM L7 (1 DUPLICATE REMOVED)
L9            19 DUP REM L2 (18 DUPLICATES REMOVED)
L10        41652 S (MODULAT? OR INHIBIT? OR ACTIVAT?)AND L6
L11           17 S L2 AND L10
L12            8 DUP REM L11 (9 DUPLICATES REMOVED)
                 E LOGRASSO P/AU
L13          175 S E3-E7
                 E HAWKINS J/AU
L14          540 S E3
                 E LISNOCK J M/AU
L15           25 S E3-E5
L16          716 S L13 OR L14 OR L15
L17            2 S L2 AND L16
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 NEWS  6  MAY 11   KOREAPAT updates resume
 NEWS  7  MAY 19   Derwent World Patents Index to be reloaded and enhanced
 NEWS  8  MAY 30   IPC 8 Rolled-up Core codes added to CA/CAplus and
                   USPATFULL/USPAT2
 NEWS  9  MAY 30   The F-Term thesaurus is now available in CA/CAplus
 NEWS 10  JUN 02   The first reclassification of IPC codes now complete in
                   INPADOC
 NEWS 11  JUN 26   TULSA/TULSA2 reloaded and enhanced with new search and
                   and display fields
 NEWS 12  JUN 28   Price changes in full-text patent databases EPFULL and PCTFULL
 NEWS 13  JUl 07   Coverage of Research Disclosure reinstated in DWPI
 NEWS 14  JUl 11   CHEMSAFE reloaded and enhanced

 NEWS EXPRESS  JUNE 30 CURRENT WINDOWS VERSION IS V8.01b, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 26 JUNE 2006.

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FILE 'HOME' ENTERED AT 16:11:16 ON 13 JUL 2006

=> file medline embase biosis biotechds scisearch hcaplus ntis lifesci
COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                     ENTRY    SESSION
FULL ESTIMATED COST                                   0.21       0.21

FILE 'MEDLINE' ENTERED AT 16:11:42 ON 13 JUL 2006

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FILE 'BIOTECHDS' ENTERED AT 16:11:42 ON 13 JUL 2006

FILE 'SCISEARCH' ENTERED AT 16:11:42 ON 13 JUL 2006

FILE 'HCAPLUS' ENTERED AT 16:11:42 ON 13 JUL 2006

FILE 'NTIS' ENTERED AT 16:11:42 ON 13 JUL 2006

FILE 'LIFESCI' ENTERED AT 16:11:42 ON 13 JUL 2006


```
=> s mitogen (w)activated (3w) kinase##
L1      149956 MITOGEN (W) ACTIVATED (3W) KINASE##

=> s MAPKAP-2
L2          37 MAPKAP-2

=> s l1 or l2
L3      149966 L1 OR L2

=> s clon? or exporess? or recombinant
<------User Break------>

=> s clon? or express? or recombinant
L4     7784549 CLON? OR EXPRESS? OR RECOMBINANT

=> s l3 and l4
L5       85357 L3 AND L4

=> s human and l5
L6       41653 HUMAN AND L5

=> s "M
MISMATCHED QUOTE '"M'
Quotation marks (or apostrophes) must be used in pairs,
one before and one after the expression you are setting
off or masking.

=> s l2 (w)kinase?
L7           5 L2 (W) KINASE?

=> dup rem l7
PROCESSING COMPLETED FOR L7
L8             4 DUP REM L7 (1 DUPLICATE REMOVED)

=> d 1-4 ibib ab

L8   ANSWER 1 OF 4  HCAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2005:141038  HCAPLUS
DOCUMENT NUMBER:          142:240427
```

TITLE: 1H-indazole-3-carboxamide compounds as MAPKAP kinase modulators and their preparation
INVENTOR(S): Wyatt, Paul Graham; Gill, Adrian Liam; Saxty, Gordon; Apaya, Robert
PATENT ASSIGNEE(S): Astex Technology Limited, UK
SOURCE: PCT Int. Appl., 107 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005014554	A1	20050217	WO 2004-GB3388	20040806

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2003-18719 A 20030808
US 2004-543496P P 20040211
OTHER SOURCE(S): CASREACT 142:240427; MARPAT 142:240427
AB The invention is related to the use of compds. I and their salts, solvates (e.g. hydrates), and N-oxides [wherein A = a bond, CH2; R1 = 3-12-membered carbocyclic or heterocyclic ring; R3, R4, R5, R6 = independently H, halo, OH, CF3, NO2, NH2, CN, etc.]in the prophylaxis or treatment of a disease state or condition mediated by a MAPKAP kinase. The invention is also related to the preparation of compds. I. For example, Pd-coupling of N-[4-[(methylaminosulfonyl)methyl]phenyl]-5-iodo-1H-indazole-3-carboxamide (preparation given) with furan-2-ylboronic acid gave 37% II. Selected I had IC50 values < 150 μM or provided at least 25% inhibition of the MAPKAP K-2 kinase activity at a concentration of 100 μM.
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:71068 HCAPLUS
DOCUMENT NUMBER: 142:150832
TITLE: Novel inhibitors of mammalian YAK3 and/or MAPKAP-2 kinases for treating various disorders
INVENTOR(S): Sato, Hideyuki; Takada, Mio; Washio, Yoshiaki
PATENT ASSIGNEE(S): Smithkline Beecham Corporation, USA
SOURCE: PCT Int. Appl., 52 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005007092	A2	20050127	WO 2004-US21701	20040707
WO 2005007092	A3	20050609		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,

LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE,
SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,
SN, TD, TG

EP 1641766 A2 20060405 EP 2004-777657 20040707
R: LT, LV, HR
PRIORITY APPLN. INFO.: US 2003-485365P P 20030708
WO 2004-US21701 W 20040707
OTHER SOURCE(S): CASREACT 142:150832; MARPAT 142:150832

AB This invention relates to newly identified inhibitors of YAK3 and/or MAPKAP-2 (MK2) kinases in mammal for treating various disorders, i.e.: neutropenia; cytopenia; anemias, including anemias due to renal insufficiency or to a chronic disease, such as autoimmunity or cancer, and drug-induced anemias; polycythemia; myelosuppression; rheumatoid arthritis; COPD; asthma; psoriasis; acute neuronal injury; heart failure; stroke, osteoarthritis; and ischemia reperfusion injury. Preparation of various inhibitors of YAK3 and/or MK2 kinases is described.

L8 ANSWER 3 OF 4 BIOTECHDS COPYRIGHT 2006 THE THOMSON CORP. on STN
DUPLICATE 1
ACCESSION NUMBER: 2003-08555 BIOTECHDS
TITLE: New isolated nucleic acid molecule encoding a human mitogen-activated protein kinase activating protein kinase-2 (MAPKAP-2), useful for treating immune-system related disorders, inflammation and arthritis;
recombinant enzyme protein production and sense and antisense sequence for use in gene therapy
AUTHOR: LOGRASSO P; HAWKINS J; LISNOCK J M
PATENT ASSIGNEE: MERCK and CO INC
PATENT INFO: WO 2002090524 14 Nov 2002
APPLICATION INFO: WO 2002-US5670 25 Feb 2002
PRIORITY INFO: US 2001-272260 28 Feb 2001; US 2001-272260 28 Feb 2001
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2003-111970 [10]

AB DERWENT ABSTRACT:
NOVELTY - An isolated nucleic acid molecule (I) comprising a sequence of nucleotides that encode a human mitogen-activated protein kinase activating protein kinase-2 (MAPKAP-2 kinase), and a coding region that encodes a splice variant of a MAPKAP -2 kinase, is new.
DETAILED DESCRIPTION - The nucleotide is selected from sequences that: (a) Encode a human MAPKAP-2 kinase and comprise a sequence of 1191 (S1) or 1203 (S2) bp given in the specification; (b) Encode a human MAPKAP-2 kinase and hybridize under conditions of high stringency to the complement of S1 or S2, and, if it is DNA, is fully complementary, or if its is RNA, is identical to mRNA native to a human cell; (c) Degenerate with the MAPKAP-2 polypeptide and encode sequence of (a) or (b); and (d) Encode a sequence having 396 (S3) or 400 (S4) amino acids given in the specification. INDEPENDENT CLAIMS are also included for the following: (1) A polypeptide (II) comprising (S3), or a variant at least 80% identical to (S3) and differs from (S3) only in one or more amino acid substitutions, additions of terminal amino acid residues and/or deletions of terminal amino acid residues, where the ability to phosphorylate Hsp-27 is not diminished; (2) Host cells (III) transfected or transformed with (I), where the cells are bacterial cells, mammalian cells or amphibian oocytes and the nucleic acid molecule is heterologous to the cells; (3) Detecting (M1) MAPKAP-2 messenger RNA in a biological sample; (4) Identifying (M2) DNA sequences encoding a MAPKAP-2

kinase; (5) Identifying (M3) MAPKAP-2 kinase in a sample; (6) Bioassay (M4) for identifying a compound or reagent which modulates activity of human MAPKAP-2 kinase; (7) Monitoring (M5) the effectiveness of a treatment with a test compound for MAPKAP-2-mediated disease state; (8) Determining (M6) regression, progression or onset of a disease state manifested by a dysfunctional signal transducing MAPKAP-2 kinase;(9) Screening (M7) test compounds for use as inflammation inhibitors;(10) Monitoring (M8) the efficacy of an agent in correcting an abnormal level of the above polypeptide in a prone subject; (11) Identifying (M9) ligand(s) that activate a MAPKAP-2 kinase; (12) An antibody specific for the gene product of (I); (13) A recombinant non-human cell line that has been engineered to express a heterologous protein, comprising (III); (14) An expression vector comprising (I) operably linked to a regulatory nucleotide sequence that controls the expression of the nucleic acid molecule; (15) Detecting (M10) a binding partner for a MAPKAP-2 kinase in a sample suspected of having the binding partner; (16) Identifying (M11) a compound which modulates the binding or kinase activity of a kinase polypeptide having S2; (17) Modulating (M12) endogenous signal transducing activity of the MAPKAP-2 kinase in a mammal; (18) Identifying (M13) a compound which modulates the binding or kinase activity of a naturally-occurring allelic variant of the polypeptide in (S3); (19) Phosphorylating (M14) a serine-containing substrate; (20) Identifying (M15) a reagent that modulates MAPKAP-2 activity; (21) Identifying (M16) a reagent that modulates MAPKAP-2 synthesis; (22) Identifying (M17) a reagent that modulates MAPKAP-2 expression; (23) Treating (M18) a subject having a disorder associated with aberrant MAPKAP-2 kinase or nucleic acid expression or activity; and (24) Kits for detecting MAPKAP-2 or the nucleic acid molecule, comprising: (a) a buffer and a labeled antibody which specifically binds to a MAPKAP-2 kinase having serine, threonine, and tyrosine kinase activity, where the sample to be tested is mixed with the buffer and the antibody; or (b) a buffer and a nucleic acid molecule comprising at least about 20 nucleotides capable of hybridizing to a nucleic acid sequence encoding MAPKAP-2 or its complement under stringent hybridization conditions, and instructions for use.

BIOTECHNOLOGY - Preparation: The nucleic acid was prepared using standard isolation techniques. Preferred Nucleic Acid: The isolated nucleic acid molecule is cDNA. The nucleic acid molecule may also comprise a nucleotide sequence encoding a polypeptide that has at least 80% identity to S3, where the 80% identity defines the amino acid alterations allowed for S3 which are determined by the equation: Na = Xa-(XaY); Na = maximum number of amino acid alterations; Xa = total number of amino acids in S3; and Y = a value of 0.80 Any non-integer product of Xa and Y is rounded down to the nearest integer prior to subtracting the product from Xa. The nucleic acid molecule has a sequence that is at least 80% identical to a nucleotide sequence encoding the above polypeptide. Preferred Polypeptide: (II) is a human MAPKAP -2 kinase encoded by (I) or a splice variant that encodes a MAPKAP-2 kinase comprising (S3) or by a nucleotide acid molecule comprising a sequence that hybridizes to the complement of (S1). Preferred Method: (M1) comprises introducing (I) into a host cell suspected of expressing a MAPKAP-2 kinase to form a complex, and detecting the presence of the complex. In (M2), identifying DNA sequences encoding a MAPKAP-2 kinase comprises probing a cDNA library or a genomic library with a labeled probe, and recovering from the library those sequences having a significant degree of homology relative to the probe, where the probe comprises (I). (M3) comprises introducing (I) into eukaryotic cells, and detecting second messenger activity in the cells, where the activity is mediated by a polypeptide encoded by (I). The bioassay (M4) for identifying a test compound which modulates the

activity of a human MAPKAP-2 kinase,
comprises: (a) measuring the second messenger activity of eukaryotic cells transformed with the DNA encoding the kinase in the absence of the test compound to obtain a first measurement; (b) measuring the second messenger activity of the eukaryotic cells in the presence of the test compound to obtain a second measurement; and (c) comparing the first and second measurements and identifying those compounds that result in a difference between the 2 measurements as a test compound that modulates the activity of the MAPKAP-2 kinase, where
the eukaryotic cells express a functional human parathyroid hormone-2 polypeptide. In (M5), monitoring comprises: (a) obtaining a pre-administration sample from a subject suspected of having a dysfunctional MAPKAP-2-mediated disease; (b) detecting a level of expression or activity of a MAPKAP-2 kinase
-encoding mRNA or genomic DNA in the pre-administration sample to obtain a first measurement; (c) detecting a level of expression or activity of the MAPKAP-2 kinase-encoding mRNA or
genomic DNA in a post-administration sample to obtain a second measurement; (d) comparing the level of expression or activity of the kinase in the first and second measurements; and (e) altering the administration of the compound to the subject accordingly. Determining (M6) regression, progression or onset of a disease state manifested by a dysfunctional signal transducing MAPKAP-2
kinase, comprises: (a) contacting a cDNA or mRNA containing
sample from a subject suspected of suffering from the disease, with the nucleic acid hybridization probe under conditions favoring binding of the probe to the cDNA or mRNA to form a complex; and (b) detecting the complex as an indication that the subject is at risk of developing the disease state. Alternatively, (M6) comprises contacting a sample from a patient with the disorder with a detectable probe that is specific for the gene product of (I), where formation of the probe/gene product complex indicates regression, progression or onset of the pathological disorder in the patient. The probe is an antibody labeled with a radioactive label or an enzyme. (M7) comprises contacting a test compound with a MAPKAP-2 kinase encoded by (I), and
testing the contacted kinase protein for its ability to bind or to phosphorylate Hsp-27, where a test compound that inhibits the binding of the MAPKAP-2 kinase protein to the Hsp-27
is a candidate drug for treating inflammation. In (M8), monitoring comprises administering the agent and determining the level of the polypeptide, where a change in the level of the polypeptide towards a normal level indicates the efficacy of the agent. Identifying (M9) ligand(s) that activate a MAPKAP-2 kinase,
comprises: (a) contacting endogenous MAPKAP-2
kinase-deficient host cells with a candidate compound suspected of activating the kinase activity, where the host cells contain a reporter gene functionally linked to a transcriptional control element; and an exogenous gene encoding the kinase, where the transcriptional control element, upon activation, induces expression of the reporter gene(s); (b) monitoring induction of the reporter gene(s); and (c) identifying ligand(s) that activate the polypeptide. (M10) comprises contacting the sample with the MAPKAP-2 under conditions favoring binding of the kinase to the binding partner, and determining the presence of the binding partner in the sample by detecting the binding of the kinase to the binding partner. In (M11), identifying comprises contacting a cell expressing the polypeptide with a test compound under conditions suitable for modulation of the binding or kinase activity of the polypeptide, and detecting the modulation of the activity or the binding of the kinase polypeptide by the test compound. Preferably, the agent inhibits or stimulates MAPKAP-2 activity, or modulates the expression of MAPKAP-2 by modulating transcription of a MAPKAP-2 gene or translation of a MAPKAP-2 mRNA. The agent may be an antibody that specifically binds to the kinase, or a nucleic acid molecule having a sequence that is antisense to the coding strand of the MAPKAP-2 mRNA or gene. (M12) comprises contacting a

cell capable of expressing MAPKAP-2 with the compound as in (M11). Modulation of the activity of the polypeptide is detected by direct binding of the test compound to the polypeptide, or by using an assay for MAPKAP-2 kinase activity (based on the phosphorylation of a MAPKAP-2 substrate). Direct binding may be determined by lysing the cell, and performing an immunoprecipitation. In addition, the direct binding may be determined by a yeast 2-hybrid assay. In (M13), the allelic variant is encoded by the nucleic acid molecule which hybridizes to the complement of a nucleic acid molecule consisting of (S1) in 6 x SSC at 45 degrees C, followed by one or more washes in 0.2 x SSC, 0.1% SDS at 50-65 degrees C, and the method comprises: (a) contacting a cell expressing the allelic variant with a test compound under conditions that modulate the binding or kinase activity of the variant; and (b) detecting modulation of the binding or kinase activity of the allelic variant by the test compound. (M14) comprises: (a) incubating the substrate with a concentration of ATP and an enzyme having at least 84% homology to (S1); and (b) measuring the amount of phosphorylation of the substrate. The method further comprises forming a mixture of the enzyme and a candidate antagonist or agonist of the enzyme, and measuring the effect of the candidate antagonist or agonist on the amount of phosphorylation of the substrate. In (M15), identifying comprises: (a) obtaining a test sample containing the MAPKAP-2 kinase and a reagent; (b) incubating the test sample with MAPKAP-2 substrate and with labeled phosphate under conditions that allow phosphorylation of the substrate; (c) determining the rate of incorporation of labeled phosphate into the substrate, where the rate of incorporation is a measure of MAPKAP-2 activity; and (d) comparing the effect of the reagent on MAPKAP-2 activity relative to a control, where a change in the activity indicates the presence of a reagent capable of modulating MAPKAP-2 activity. The MAPKAP-2 substrate is Hsp-25, Hsp-27 or ALT2. The modulation is inhibition of MAPKAP-2 activity. The reagent is an antisense oligonucleotide, a ribozyme, a tumor necrosis factor or an interleukin-1. (M16) comprises: (a) providing a test sample containing the MAPKAP-2 kinase; (b) incubating the sample in the presence of a reagent; (c) fractionating proteins present in the sample by gel electrophoresis; (d) transferring the proteins onto a membrane; (e) probing the proteins with a labeled antibody specific to the MAPKAP-2 kinase, where the level of the synthesis is determined by the amount of the antibody detected; and (f) comparing the effect of the reagent on MAPKAP-2 synthesis relative to a control, where a change in the synthesis indicates the presence of a reagent that modulates MAPKAP-2 synthesis. (M17) comprises: (a) providing a test sample in which a MAPKAP-2 polynucleotide is expressed; (b) incubating the sample in the presence of a reagent; (c) isolating polyadenylated RNA from the sample; (d) incubating the RNA with a polynucleotide probe specific for MAPKAP-2 kinase; (e) determining the amount of the probe hybridized to the RNA, where a level of expression of MAPKAP-2 is directly related to the amount of MAPKAP-2 probe hybridized to the RNA; and (f) comparing the effect of the reagent on MAPKAP-2 expression relative to a control, where a change in the expression indicates the presence of a reagent that modulates MAPKAP-2 expression. Treating (M18) a subject having a disorder associated with aberrant MAPKAP-2 kinase or nucleic acid expression or activity, comprises administering an agent which is a MAPKAP-2 modulator to the subject. The MAPKAP-2 modulator is a MAPKAP-2 kinase, MAPKAP-2 nucleic acid molecule, a peptide, a peptidomimetic, or other small molecule. The disorder is an immune-related disorder.

ACTIVITY - Immunomodulator; Antiinflammatory; Cytostatic; Antiarthritic. No biological data given.

MECHANISM OF ACTION - Gene therapy; Serine-Threonine-Kinase.

USE - (I) encodes (II) which may be used to treat an immune-related disorder (claimed). (I) is especially useful in regulating signal transduction in a cell, and in diagnosing or treating MAPKAP-2-mediated

disorders, e.g. cell proliferative disorders, immune system disorders, inflammation, arthritis. The nucleic acid and the polypeptide may also be used in screening assays, predictive medicine, diagnostic or prognostic assays, chromosome mapping, tissue typing, pharmacogenomics and in monitoring clinical trials.

ADMINISTRATION - Administration is oral, topical or parenteral (e.g. intraarterial, intramuscular, subcutaneous, intramedullary, intrathecal, intraventricular, intravenous, intraperitoneal, or intranasal). The dosage is 0.001-50 mg/kg, preferably 0.1-1.0 mg/kg.

EXAMPLE - No relevant example given.(150 pages)

L8 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:470402 HCAPLUS
DOCUMENT NUMBER: 136:83416
TITLE: Signal transduction in the adapted heart: Implication of protein kinase C-dependent and -independent pathways
AUTHOR(S): Debarros, John; Das, Dipak K.
CORPORATE SOURCE: Department of Surgery, University of Connecticut School of Medicine, Farmington, CT, 06032, USA
SOURCE: Progress in Experimental Cardiology (2000), 3(Hypertrophied Heart), 3-16
CODEN: PEXCFF; ISSN: 1389-1774
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Cardioprotection as a result of myocardial adaptation to cellular stress is a product of evolution. Myocardial adaptation potentiates intracellular signaling involving diverse signal transduction pathways. Ischemic preconditioning, a specific form of myocardial adaptive response, occurs through both G proteins and receptor tyrosine kinase. Such preconditioning, mediated by cyclic episodes of brief reversible ischemia each followed by another brief period of reperfusion, leads to improvement in infarct size and ventricular recovery. Adaptation can also be achieved through other environmental stresses, including oxidative stress. Several triggers for signal transduction have been identified, including catecholamines, bradykinin, and adenosine. The processing of stress signals from signal initiation to propagation to eventual termination is the focus of this chapter. Signal initiation occurs through G-protein as well as receptor tyrosine kinase activation. Complex signaling processes involving MAP kinases, MAPKAP kinase 2, and protein kinase C have become central to our understanding of signal propagation. Signal termination resulting in biol. expression of signal propagation by means of gene expression and transcription regulation is the ultimate outcome of cellular stress response. This chapter especially examines these complex signal transduction processes that lead to the stress response and eventual adaptation, focusing primarily upon protein kinase C-dependent and -independent pathways.
REFERENCE COUNT: 92 THERE ARE 92 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d his

(FILE 'HOME' ENTERED AT 16:11:16 ON 13 JUL 2006)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 16:11:42 ON 13 JUL 2006
L1 149956 S MITOGEN (W)ACTIVATED (3W) KINASE##
L2 37 S MAPKAP-2
L3 149966 S L1 OR L2
L4 7784549 S CLON? OR EXPRESS? OR RECOMBINANT
L5 85357 S L3 AND L4
L6 41653 S HUMAN AND L5

```
L7             5 S L2 (W)KINASE?
L8             4 DUP REM L7 (1 DUPLICATE REMOVED)

=> dup rem l2
PROCESSING COMPLETED FOR L2
L9            19 DUP REM L2 (18 DUPLICATES REMOVED)

=> d 1-19 ibib ab

L9   ANSWER 1 OF 19     MEDLINE on STN                    DUPLICATE 1
ACCESSION NUMBER:   2006074832     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 16447221
TITLE:              Activation of p38 MAPK is a key step in tumor necrosis
                    factor-mediated inflammatory bone destruction.
AUTHOR:             Zwerina Jochen; Hayer Silvia; Redlich Kurt; Bobacz Klaus;
                    Kollias Giorgos; Smolen Josef S; Schett Georg
CORPORATE SOURCE:   Medical University of Vienna, Vienna, Austria.
SOURCE:             Arthritis and rheumatism, (2006 Feb) Vol. 54, No. 2, pp.
                    463-72.
                    Journal code: 0370605. ISSN: 0004-3591.
PUB. COUNTRY:       United States
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH:        200603
ENTRY DATE:         Entered STN: 8 Feb 2006
                    Last Updated on STN: 18 Mar 2006
                    Entered Medline: 17 Mar 2006
AB   OBJECTIVE: To investigate whether activation of p38 MAPK is a crucial
     signaling factor in inflammatory bone destruction mediated by tumor
     necrosis factor (TNF). Mice overexpressing TNF were treated with 2
     different inhibitors of p38 MAPK, and the effect of this treatment on
     joint inflammation and structural damage was assessed. METHODS: Human
     TNF-transgenic mice received systemic treatment with 2 different p38 MAPK
     inhibitors (RO4399247 and AVE8677). Treatment was started at the time of
     symptom onset and lasted for 6 weeks. Mice were assessed for clinical
     signs of arthritis, bone erosion, and cartilage damage. In addition, the
     effect of these inhibitors on osteoclast generation in vitro and in vivo
     was assessed. RESULTS: Both p38 MAPK inhibitors significantly reduced
     clinical signs of TNF-mediated arthritis. This was attributable to
     reducing synovial inflammation by 50% without affecting the cellular
     composition of the infiltrate. Synovial expression of interleukin-1 and
     RANKL was reduced upon p38 MAPK blockade, and activation of the molecular
     target MAPK-activated protein kinase 2 (MAPKAP-2) was
     also inhibited. Proteoglycan loss of articular cartilage was reduced by
     50%, although p38 MAPK inhibition did not change matrix molecule synthesis
     by cultivated chondrocytes. Importantly, bone loss was almost completely
     prevented by p38 MAPK inhibition. The numbers of synovial osteoclasts and
     precursors were dramatically reduced, and both p38 MAPK inhibitors also
     inhibited in vitro osteoclastogenesis at micromolar concentrations and
     blocked activation of MAPKAP-2 as well as
     differentiation markers in cultured osteoclast precursors. CONCLUSION:
     These results suggest the major importance of p38 MAPK for TNF-mediated
     inflammatory bone destruction in arthritis and suggest that inhibition of
     p38 MAPK might be an important tool for reducing structural damage in
     rheumatoid arthritis.

L9   ANSWER 2 OF 19  HCAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:        2005:141038  HCAPLUS
DOCUMENT NUMBER:         142:240427
TITLE:                   1H-indazole-3-carboxamide compounds as MAPKAP kinase
                         modulators and their preparation
INVENTOR(S):             Wyatt, Paul Graham; Gill, Adrian Liam; Saxty, Gordon;
                         Apaya, Robert
```

PATENT ASSIGNEE(S): Astex Technology Limited, UK
SOURCE: PCT Int. Appl., 107 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005014554	A1	20050217	WO 2004-GB3388	20040806

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2003-18719 A 20030808
US 2004-543496P P 20040211
OTHER SOURCE(S): CASREACT 142:240427; MARPAT 142:240427

AB The invention is related to the use of compds. I and their salts, solvates (e.g. hydrates), and N-oxides [wherein A = a bond, CH2; R1 = 3-12-membered carbocyclic or heterocyclic ring; R3, R4, R5, R6 = independently H, halo, OH, CF3, NO2, NH2, CN, etc.]in the prophylaxis or treatment of a disease state or condition mediated by a MAPKAP kinase. The invention is also related to the preparation of compds. I. For example, Pd-coupling of N-[4-[(methylaminosulfonyl)methyl]phenyl]-5-iodo-1H-indazole-3-carboxamide (preparation given) with furan-2-ylboronic acid gave 37% II. Selected I had IC50 values < 150 μM or provided at least 25% inhibition of the MAPKAP K-2 kinase activity at a concentration of 100 μM.

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 3 OF 19 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:71068 HCAPLUS
DOCUMENT NUMBER: 142:150832
TITLE: Novel inhibitors of mammalian YAK3 and/or MAPKAP-2 kinases for treating various disorders
INVENTOR(S): Sato, Hideyuki; Takada, Mio; Washio, Yoshiaki
PATENT ASSIGNEE(S): Smithkline Beecham Corporation, USA
SOURCE: PCT Int. Appl., 52 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005007092	A2	20050127	WO 2004-US21701	20040707
WO 2005007092	A3	20050609		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,

AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1641766 A2 20060405 EP 2004-777657 20040707
R: LT, LV, HR

PRIORITY APPLN. INFO.: US 2003-485365P P 20030708
WO 2004-US21701 W 20040707

OTHER SOURCE(S): CASREACT 142:150832; MARPAT 142:150832

AB This invention relates to newly identified inhibitors of YAK3 and/or MAPKAP-2 (MK2) kinases in mammal for treating various disorders, i.e.: neutropenia; cytopenia; anemias, including anemias due to renal insufficiency or to a chronic disease, such as autoimmunity or cancer, and drug-induced anemias; polycythemia; myelosuppression; rheumatoid arthritis; COPD; asthma; psoriasis; acute neuronal injury; heart failure; stroke, osteoarthritis; and ischemia reperfusion injury. Preparation of various inhibitors of YAK3 and/or MK2 kinases is described.

L9 ANSWER 4 OF 19 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:1083178 HCAPLUS
DOCUMENT NUMBER: 144:167719
TITLE: Cholesterol is the major component of native lipoproteins activating the p38 mitogen-activated protein kinases
AUTHOR(S): Dobreva, Iveta; Zschornig, Olaf; Waeber, Gerard; James, Richard W.; Widmann, Christian
CORPORATE SOURCE: Departement de Biologie Cellulaire et de Morphologie (DBCM), Universite de Lausanne, Lausanne, CH-1005, Switz.
SOURCE: Biological Chemistry (2005), 386(9), 909-918
CODEN: BICHF3; ISSN: 1431-6730
PUBLISHER: Walter de Gruyter GmbH & Co. KG
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Elevated low-d. lipoprotein (LDL) levels induce activation of the p38 mitogen-activated protein kinase (MAPK), a stress-activated protein kinase potentially participating in the development of atherosclerosis. The nature of the lipoprotein components inducing p38 MAPK activation has remained unclear however. We show here that both LDLs and high-d. lipoproteins (HDLs) have the ability to stimulate the p38 MAPKs with potencies that correlate with their cholesterol content. Cholesterol solubilized in methyl-β-cyclodextrin was sufficient to activate the p38 MAPK pathway. Liposomes made of phosphatidylcholine (PC) or sphingomyelin, the two main phospholipids found in lipoproteins, were unable to stimulate the p38 MAPKs. In contrast, PC liposomes loaded with cholesterol potently activated this pathway. Reducing the cholesterol content of LDL particles lowered their ability to activate the p38 MAPKs. Cell lines representative of the three main cell types found in blood vessels (endothelial cells, smooth muscle cells and fibroblasts) all activated their p38 MAPK pathway in response to LDLs or cholesterol-loaded PC liposomes. These results indicate that elevated cholesterol content in lipoproteins, as seen in hypercholesterolemia, favors the activation of the stress-activated p38 MAPK pathway in cells from the vessel wall, an event that might contribute to the development of atherosclerosis.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 5 OF 19 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2006:211940 BIOSIS
DOCUMENT NUMBER: PREV200600209039
TITLE: Doxorubicin induced toxicity in cardiac cells is attenuated by p38MAPK and phosphorylation of small heat shock proteins.
AUTHOR(S): Venkatakrishnan, C . D. [Reprint Author]; Tiwari, Arun;

Moldovan, Leni; Zweier, Jay; Kuppusamy, Periannan; Ilangovan, Govindasamy
CORPORATE SOURCE: Ohio State Univ, Davis Heart and Lung Res Inst, Columbus, OH 43210 USA
SOURCE: Free Radical Biology & Medicine, (2005) Vol. 39, No. Suppl. 1, pp. S171.
Meeting Info.: 12th Annual Meeting Society-for-Free-Radical-Biology-and-Medicine. Austin, TX, USA. November 16 -20, 2005. Soc Free Rad Biol & Med.
CODEN: FRBMEH. ISSN: 0891-5849.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 29 Mar 2006
Last Updated on STN: 29 Mar 2006

L9 ANSWER 6 OF 19 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2006:2430 BIOSIS
DOCUMENT NUMBER: PREV200600001220
TITLE: P38 inhibition ameliorates TNF-mediated arthritis.
AUTHOR(S): Zwerina, J. [Reprint Author]; Hayer, S.; Redlich, K.; Smolen, J.; Schett, G.
CORPORATE SOURCE: Med Univ Vienna, Dept Internal Med 3, Div Rheumatol, Vienna, Austria
SOURCE: Annals of the Rheumatic Diseases, (JUL 2005) Vol. 64, No. Suppl. 3, pp. 170-171.
Meeting Info.: Annual European Congress of Rheumatology. Vienna, AUSTRIA. June 08 -11, 2005.
CODEN: ARDIAO. ISSN: 0003-4967.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 14 Dec 2005
Last Updated on STN: 14 Dec 2005

L9 ANSWER 7 OF 19 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2006:5597 BIOSIS
DOCUMENT NUMBER: PREV200600003110
TITLE: Activation of p38MAPK is a key step in TNF-Mediated inflammatory bone destruction.
AUTHOR(S): Zwerina, Jochen [Reprint Author]; Hayer, Silvia; Redlich, Kurt; Bobacz, Klaus; Smolen, Josef S.; Schett, Georg
CORPORATE SOURCE: Med Univ Vienna, Vienna, Austria
SOURCE: Arthritis & Rheumatism, (SEP 2005) Vol. 52, No. 9, Suppl. S, pp. S160.
Meeting Info.: 69th Annual Scientific Meeting of the American-College-of-Rheumatology/40th Annual Scientific Meeting of the Association-of-Rheumatology-Health-Professionals. San Diego, CA, USA. November 12 -17, 2005. Amer Coll Rheumatol; Assoc Rheumatol Hlth Profess.
CODEN: ARHEAW. ISSN: 0004-3591.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 14 Dec 2005
Last Updated on STN: 14 Dec 2005

L9 ANSWER 8 OF 19 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2004461604 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15371522
TITLE: MAP kinases and cell migration.
AUTHOR: Huang Cai; Jacobson Ken; Schaller Michael D
CORPORATE SOURCE: Department of Cell and Developmental Biology, University of North Carolina, Chapel Hill, NC 27599-7090, USA.

SOURCE: Journal of cell science, (2004 Sep 15) Vol. 117, No. Pt 20, pp. 4619-28. Ref: 131
Journal code: 0052457. ISSN: 0021-9533.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200510
ENTRY DATE: Entered STN: 17 Sep 2004
Last Updated on STN: 19 Dec 2004
Entered Medline: 18 Oct 2005

AB Recent studies have demonstrated that mitogen-activated protein kinases (MAPKs), including Jun N-terminus kinase (JNK), p38 and Erk, play crucial roles in cell migration. JNK, for example, regulates cell migration by phosphorylating paxillin, DCX, Jun and microtubule-associated proteins. Studies of p38 show that this MAPK modulates migration by phosphorylating MAPK-activated protein kinase 2/3 (MAPKAP 2/3), which appears to be important for directionality of migration. Erk governs cell movement by phosphorylating myosin light chain kinase (MLCK), calpain or FAK. Thus, the different kinases in the MAPK family all seem able to regulate cell migration but by distinct mechanisms.

L9 ANSWER 9 OF 19 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2004013081 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14694199
TITLE: Differentiation stage-specific activation of p38 mitogen-activated protein kinase isoforms in primary human erythroid cells.
AUTHOR: Uddin Shahab; Ah-Kang Jeong; Ulaszek Jodie; Mahmud Dolores; Wickrema Amittha
CORPORATE SOURCE: Section of Hematology/Oncology, University of Chicago, Chicago, IL 60637, USA.
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (2004 Jan 6) Vol. 101, No. 1, pp. 147-52. Electronic Publication: 2003-12-23.
Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200402
ENTRY DATE: Entered STN: 8 Jan 2004
Last Updated on STN: 2 Mar 2004
Entered Medline: 25 Feb 2004

AB p38alpha, p38beta, p38gamma, and p38delta are four isoforms of p38 mitogen-activated protein (MAP) kinase (MAPK) involved in multiple cellular functions such as cell proliferation, differentiation, apoptosis, and inflammation response. In the present study, we examined the mRNA expression pattern of each of the four isoforms during erythroid differentiation of primary erythroid progenitors. We show that p38alpha and p38gamma transcripts are expressed in early hematopoietic progenitors as well as in late differentiating erythroblasts, whereas p38delta mRNA is only expressed and active during the terminal phase of erythroid differentiation. On the other hand, p38beta is minimally expressed in early CD34(+) hematopoietic progenitors but not expressed in lineage-committed erythroid progenitors. We also determined the phosphorylation/activation of p38alpha, MAPK kinase 3/6, and MAPKAP-2 in response to erythropoietin and stem cell factor. We found that phosphorylation of p38alpha, MAPK kinase kinase 3/6 and MAPKAP-2 occurs only upon growth factor withdrawal in primary erythroid progenitors. Moreover, our data indicate that activation of p38alpha does not induce apoptosis or promote proliferation of erythroid progenitors. On the other hand, under steady-state culture

conditions, both p38alpha and p38delta isoforms are increasingly phosphorylated activated in the terminal phase of differentiation. This increased phosphorylation/activity was accompanied by up-regulation of heat shock protein 27 phosphorylation. Finally, we demonstrate that tumor necrosis factor alpha, an inflammatory cytokine that is modulated by p38alpha, is expressed by differentiating erythroblasts and inhibition of p38alpha or tumor necrosis factor alpha results in reduction in differentiation. Taken together, our data demonstrate that both p38alpha and delta isoforms function to promote the late-stage differentiation of primary erythroid progenitors and are likely to be involved in functions related to erythrocyte membrane remodeling and enucleation.

L9 ANSWER 10 OF 19 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2003:440551 BIOSIS
DOCUMENT NUMBER: PREV200300440551
TITLE: Stage specific expression of p38 kinase isoforms regulates erythroid differentiation in primary erythroid progenitors.
AUTHOR(S): Uddin, S. [Reprint Author]; Kang, J. H. [Reprint Author]; Ulaszek, J.; Mahmud, D. [Reprint Author]; Wickrema, A. [Reprint Author]
CORPORATE SOURCE: Hematology, University of Chicago, Chicago, IL, USA
SOURCE: Experimental Hematology (New York), (July 2003) Vol. 31, No. 7 Supplement 1, pp. 160. print.
Meeting Info.: 32nd Annual Meeting of the International Society for Experimental Hematology. Paris, France. July 05-08, 2003.
ISSN: 0301-472X (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Sep 2003
Last Updated on STN: 24 Sep 2003

L9 ANSWER 11 OF 19 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2004:92761 BIOSIS
DOCUMENT NUMBER: PREV200400085953
TITLE: Cantharidin (CAN) protects against glucose-induced podocyte actin-cytoskeletal disruption.
AUTHOR(S): Tong, Li-Li [Reprint Author]; Sim, John J. [Reprint Author]; Chang, Roger [Reprint Author]; Chuang, Peter [Reprint Author]; Lapage, Janine [Reprint Author]; Wang, S. [Reprint Author]; Dennis, Wu [Reprint Author]; Nast, Cynthia C.; Natarajan, Rama; Adler, Sharon G. [Reprint Author]
CORPORATE SOURCE: Nephrology, Harbor-UCLA Research and Education Institute, Torrance, CA, USA
SOURCE: Journal of the American Society of Nephrology, (November 2003) Vol. 14, No. Abstracts Issue, pp. 93A. print.
Meeting Info.: Meeting of the American Society of Nephrology Renal Week. San Diego, CA, USA. November 12-17, 2003. American Society of Nephrology.
CODEN: JASNEU. ISSN: 1046-6673.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 11 Feb 2004
Last Updated on STN: 11 Feb 2004

L9 ANSWER 12 OF 19 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2004:180903 BIOSIS

DOCUMENT NUMBER: PREV200400180952
TITLE: Quantitative proteomic and genomic analysis of p38 MAPK signaling in transformed follicular lymphoma cells.
AUTHOR(S): Lin, Zhaosheng [Reprint Author]; Crockett, David K. [Reprint Author]; Jenson, Stephen D.; Lim, Megan S. [Reprint Author]; Elenitoba-Johnson, Kojo S. J. [Reprint Author]
CORPORATE SOURCE: Molecular Hematopathology, ARUP Institute for Clinical and Experimental Pathology, Salt Lake City, UT, USA
SOURCE: Blood, (November 16 2003) Vol. 102, No. 11, pp. 24a-25a. print.
Meeting Info.: 45th Annual Meeting of the American Society of Hematology. San Diego, CA, USA. December 06-09, 2003. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 7 Apr 2004
Last Updated on STN: 7 Apr 2004

AB The p38 mitogen-activated protein kinase (p38 MAPK) is a key mediator of extracellular growth factor and cytokine induced signaling pathways and has been implicated in the development of some human cancers. Our previous work showed evidence for p38 MAPK activation in a subset of transformed follicular lymphomas (Elenitoba-Johnson, et al. PNAS 2003; 100;7259). We further demonstrated that inhibition of p38 MAPK, using the pyridinyl imidazole inhibitor SB203580 resulted in dose- and time-dependent caspase 3-mediated apoptosis. In order to further elucidate the role of p38 MAPK in follicular lymphoma transformation, we have employed a systems biologic approach involving transcriptional profiling and quantitative proteomic analysis of transformed follicular lymphoma derived-cells (OCI-Ly1) treated with SB203580. Cultured OCI-Ly1 cells expressing native and phosphorylated-p38 MAPK were exposed to SB203580, and significant growth inhibition was achieved after 3 hours as determined by in vitro MTT (3-(4,5-dimethyl thiazol-2-yl)-2,5-diphenyl tetrazolium bromide) assays. Direct comparison of the transcriptomes of treated versus untreated cells at 3 and 21 hours was performed using a cDNA array format containing 9600 genes. Quantitative proteomic analysis was performed using cleavable isotope-coded affinity tags (ICATTM) and three-dimensional (strong cationic exchange, affinity and reverse-phase) chromatographic separation followed by tandem mass spectrometry. Gene expression profiling revealed differential expression (ltoreqor gtoreq1.5-fold) of 386 genes and ESTs in cells treated for 3 hours, and 532 genes and ESTs in cells treated for 21 hours. Majority of these genes and ESTs (52% for 3 hours and 91% for 21 hours) were downregulated in response to p38 MAPK inhibition, including genes encoding growth cytokines, transcriptional regulators and cytoskeletal proteins. Quantitative proteomic analysis unequivocally identified (XCorr values gtoreq2.0 for all cysteine containing peptides with DCn gtoreq0.1) 277 differentially expressed proteins at 3 hours and 350 proteins at 21 hours of treatment with SB203580., Consistent with the results of microarray analysis, 82% of the differentially expressed proteins were down-regulated at 3 hours and 76% at 21 hours. Analysis of functional groups of the differentially expressed proteins implicated components of diverse overlapping pathways including the IL-6/PI-3K, IGF-2/Ras/Raf, WNT8d/Frizzled, MAPKAP-2 and NFk B in p38 MAPK signaling. Our studies reveal the global cellular ramifications of p38 MAPK-mediated cellular signaling and its potential role in the pathogenesis of follicular lymphoma transformation. Furthermore, our results demonstrate the complementary nature of genomic and proteomic approaches in the evaluation of signal transduction pathways.

L9 ANSWER 13 OF 19 BIOTECHDS COPYRIGHT 2006 THE THOMSON CORP. on STN
DUPLICATE 4

ACCESSION NUMBER: 2003-08555 BIOTECHDS
TITLE: New isolated nucleic acid molecule encoding a human mitogen-activated protein kinase activating protein kinase-2 (MAPKAP-2), useful for treating immune-system related disorders, inflammation and arthritis; recombinant enzyme protein production and sense and antisense sequence for use in gene therapy
AUTHOR: LOGRASSO P; HAWKINS J; LISNOCK J M
PATENT ASSIGNEE: MERCK and CO INC
PATENT INFO: WO 2002090524 14 Nov 2002
APPLICATION INFO: WO 2002-US5670 25 Feb 2002
PRIORITY INFO: US 2001-272260 28 Feb 2001; US 2001-272260 28 Feb 2001
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2003-111970 [10]

AB DERWENT ABSTRACT:
NOVELTY - An isolated nucleic acid molecule (I) comprising a sequence of nucleotides that encode a human mitogen-activated protein kinase activating protein kinase-2 (MAPKAP-2 kinase), and a coding region that encodes a splice variant of a MAPKAP-2 kinase, is new.

DETAILED DESCRIPTION - The nucleotide is selected from sequences that: (a) Encode a human MAPKAP-2 kinase and comprise a sequence of 1191 (S1) or 1203 (S2) bp given in the specification; (b) Encode a human MAPKAP-2 kinase and hybridize under conditions of high stringency to the complement of S1 or S2, and, if it is DNA, is fully complementary, or if its is RNA, is identical to mRNA native to a human cell; (c) Degenerate with the MAPKAP-2 polypeptide and encode sequence of (a) or (b); and (d) Encode a sequence having 396 (S3) or 400 (S4) amino acids given in the specification. INDEPENDENT CLAIMS are also included for the following: (1) A polypeptide (II) comprising (S3), or a variant at least 80% identical to (S3) and differs from (S3) only in one or more amino acid substitutions, additions of terminal amino acid residues and/or deletions of terminal amino acid residues, where the ability to phosphorylate Hsp-27 is not diminished; (2) Host cells (III) transfected or transformed with (I), where the cells are bacterial cells, mammalian cells or amphibian oocytes and the nucleic acid molecule is heterologous to the cells; (3) Detecting (M1) MAPKAP-2 messenger RNA in a biological sample; (4) Identifying (M2) DNA sequences encoding a MAPKAP-2 kinase; (5) Identifying (M3) MAPKAP-2 kinase in a sample; (6) Bioassay (M4) for identifying a compound or reagent which modulates activity of human MAPKAP-2 kinase; (7) Monitoring (M5) the effectiveness of a treatment with a test compound for MAPKAP-2-mediated disease state; (8) Determining (M6) regression, progression or onset of a disease state manifested by a dysfunctional signal transducing MAPKAP-2 kinase;(9) Screening (M7) test compounds for use as inflammation inhibitors;(10) Monitoring (M8) the efficacy of an agent in correcting an abnormal level of the above polypeptide in a prone subject; (11) Identifying (M9) ligand(s) that activate a MAPKAP-2 kinase; (12) An antibody specific for the gene product of (I); (13) A recombinant non-human cell line that has been engineered to express a heterologous protein, comprising (III); (14) An expression vector comprising (I) operably linked to a regulatory nucleotide sequence that controls the expression of the nucleic acid molecule; (15) Detecting (M10) a binding partner for a MAPKAP-2 kinase in a sample suspected of having the binding partner; (16) Identifying (M11) a compound which modulates the binding or kinase activity of a kinase polypeptide having S2; (17) Modulating (M12) endogenous signal transducing activity of the MAPKAP-2 kinase in a mammal; (18) Identifying (M13) a compound which modulates the binding or kinase activity of a naturally-occurring allelic variant of the polypeptide in (S3); (19) Phosphorylating (M14) a serine-containing

substrate; (20) Identifying (M15) a reagent that modulates MAPKAP -2 activity; (21) Identifying (M16) a reagent that modulates MAPKAP-2 synthesis; (22) Identifying (M17) a reagent that modulates MAPKAP-2 expression; (23) Treating (M18) a subject having a disorder associated with aberrant MAPKAP -2 kinase or nucleic acid expression or activity; and (24) Kits for detecting MAPKAP-2 or the nucleic acid molecule, comprising: (a) a buffer and a labeled antibody which specifically binds to a MAPKAP-2 kinase having serine, threonine, and tyrosine kinase activity, where the sample to be tested is mixed with the buffer and the antibody; or (b) a buffer and a nucleic acid molecule comprising at least about 20 nucleotides capable of hybridizing to a nucleic acid sequence encoding MAPKAP-2 or its complement under stringent hybridization conditions, and instructions for use.

BIOTECHNOLOGY - Preparation: The nucleic acid was prepared using standard isolation techniques. Preferred Nucleic Acid: The isolated nucleic acid molecule is cDNA. The nucleic acid molecule may also comprise a nucleotide sequence encoding a polypeptide that has at least 80% identity to S3, where the 80% identity defines the amino acid alterations allowed for S3 which are determined by the equation: Na = Xa-(XaY); Na = maximum number of amino acid alterations; Xa = total number of amino acids in S3; and Y = a value of 0.80 Any non-integer product of Xa and Y is rounded down to the nearest integer prior to subtracting the product from Xa. The nucleic acid molecule has a sequence that is at least 80% identical to a nucleotide sequence encoding the above polypeptide. Preferred Polypeptide: (II) is a human MAPKAP -2 kinase encoded by (I) or a splice variant that encodes a MAPKAP-2 kinase comprising (S3) or by a nucleotide acid molecule comprising a sequence that hybridizes to the complement of (S1). Preferred Method: (M1) comprises introducing (I) into a host cell suspected of expressing a MAPKAP-2 kinase to form a complex, and detecting the presence of the complex. In (M2), identifying DNA sequences encoding a MAPKAP-2 kinase comprises probing a cDNA library or a genomic library with a labeled probe, and recovering from the library those sequences having a significant degree of homology relative to the probe, where the probe comprises (I). (M3) comprises introducing (I) into eukaryotic cells, and detecting second messenger activity in the cells, where the activity is mediated by a polypeptide encoded by (I). The bioassay (M4) for identifying a test compound which modulates the activity of a human MAPKAP-2 kinase, comprises: (a) measuring the second messenger activity of eukaryotic cells transformed with the DNA encoding the kinase in the absence of the test compound to obtain a first measurement; (b) measuring the second messenger activity of the eukaryotic cells in the presence of the test compound to obtain a second measurement; and (c) comparing the first and second measurements and identifying those compounds that result in a difference between the 2 measurements as a test compound that modulates the activity of the MAPKAP-2 kinase, where the eukaryotic cells express a functional human parathyroid hormone-2 polypeptide. In (M5), monitoring comprises: (a) obtaining a pre-administration sample from a subject suspected of having a dysfunctional MAPKAP-2-mediated disease; (b) detecting a level of expression or activity of a MAPKAP-2 kinase-encoding mRNA or genomic DNA in the pre-administration sample to obtain a first measurement; (c) detecting a level of expression or activity of the MAPKAP-2 kinase-encoding mRNA or genomic DNA in a post-administration sample to obtain a second measurement; (d) comparing the level of expression or activity of the kinase in the first and second measurements; and (e) altering the administration of the compound to the subject accordingly. Determining (M6) regression, progression or onset of a disease state manifested by a dysfunctional signal transducing MAPKAP-2 kinase, comprises: (a) contacting a cDNA or mRNA containing sample from a subject

suspected of suffering from the disease, with the nucleic acid hybridization probe under conditions favoring binding of the probe to the cDNA or mRNA to form a complex; and (b) detecting the complex as an indication that the subject is at risk of developing the disease state. Alternatively, (M6) comprises contacting a sample from a patient with the disorder with a detectable probe that is specific for the gene product of (I), where formation of the probe/gene product complex indicates regression, progression or onset of the pathological disorder in the patient. The probe is an antibody labeled with a radioactive label or an enzyme. (M7) comprises contacting a test compound with a MAPKAP -2 kinase encoded by (I), and testing the contacted kinase protein for its ability to bind or to phosphorylate Hsp-27, where a test compound that inhibits the binding of the MAPKAP-2 kinase protein to the Hsp-27 is a candidate drug for treating inflammation. In (M8), monitoring comprises administering the agent and determining the level of the polypeptide, where a change in the level of the polypeptide towards a normal level indicates the efficacy of the agent. Identifying (M9) ligand(s) that activate a MAPKAP-2 kinase, comprises: (a) contacting endogenous MAPKAP-2 kinase-deficient host cells with a candidate compound suspected of activating the kinase activity, where the host cells contain a reporter gene functionally linked to a transcriptional control element; and an exogenous gene encoding the kinase, where the transcriptional control element, upon activation, induces expression of the reporter gene(s); (b) monitoring induction of the reporter gene(s); and (c) identifying ligand(s) that activate the polypeptide. (M10) comprises contacting the sample with the MAPKAP-2 under conditions favoring binding of the kinase to the binding partner, and determining the presence of the binding partner in the sample by detecting the binding of the kinase to the binding partner. In (M11), identifying comprises contacting a cell expressing the polypeptide with a test compound under conditions suitable for modulation of the binding or kinase activity of the polypeptide, and detecting the modulation of the activity or the binding of the kinase polypeptide by the test compound. Preferably, the agent inhibits or stimulates MAPKAP-2 activity, or modulates the expression of MAPKAP-2 by modulating transcription of a MAPKAP-2 gene or translation of a MAPKAP-2 mRNA. The agent may be an antibody that specifically binds to the kinase, or a nucleic acid molecule having a sequence that is antisense to the coding strand of the MAPKAP-2 mRNA or gene. (M12) comprises contacting a cell capable of expressing MAPKAP-2 with the compound as in (M11). Modulation of the activity of the polypeptide is detected by direct binding of the test compound to the polypeptide, or by using an assay for MAPKAP-2 kinase activity (based on the phosphorylation of a MAPKAP-2 substrate). Direct binding may be determined by lysing the cell, and performing an immunoprecipitation. In addition, the direct binding may be determined by a yeast 2-hybrid assay. In (M13), the allelic variant is encoded by the nucleic acid molecule which hybridizes to the complement of a nucleic acid molecule consisting of (S1) in 6 x SSC at 45 degrees C, followed by one or more washes in 0.2 x SSC, 0.1% SDS at 50-65 degrees C, and the method comprises: (a) contacting a cell expressing the allelic variant with a test compound under conditions that modulate the binding or kinase activity of the variant; and (b) detecting modulation of the binding or kinase activity of the allelic variant by the test compound. (M14) comprises: (a) incubating the substrate with a concentration of ATP and an enzyme having at least 84% homology to (S1); and (b) measuring the amount of phosphorylation of the substrate. The method further comprises forming a mixture of the enzyme and a candidate antagonist or agonist of the enzyme, and measuring the effect of the candidate antagonist or agonist on the amount of phosphorylation of the substrate. In (M15), identifying comprises: (a) obtaining a test sample containing the MAPKAP-2 kinase and a reagent; (b) incubating the test

sample with MAPKAP-2 substrate and with labeled phosphate under conditions that allow phosphorylation of the substrate; (c) determining the rate of incorporation of labeled phosphate into the substrate, where the rate of incorporation is a measure of MAPKAP -2 activity; and (d) comparing the effect of the reagent on MAPKAP-2 activity relative to a control, where a change in the activity indicates the presence of a reagent capable of modulating MAPKAP-2 activity. The MAPKAP-2 substrate is Hsp-25, Hsp-27 or ALT2. The modulation is inhibition of MAPKAP-2 activity. The reagent is an antisense oligonucleotide, a ribozyme, a tumor necrosis factor or an interleukin-1. (M16) comprises: (a) providing a test sample containing the MAPKAP-2 kinase; (b) incubating the sample in the presence of a reagent; (c) fractionating proteins present in the sample by gel electrophoresis; (d) transferring the proteins onto a membrane; (e) probing the proteins with a labeled antibody specific to the MAPKAP-2 kinase, where the level of the synthesis is determined by the amount of the antibody detected; and (f) comparing the effect of the reagent on MAPKAP-2 synthesis relative to a control, where a change in the synthesis indicates the presence of a reagent that modulates MAPKAP-2 synthesis. (M17) comprises: (a) providing a test sample in which a MAPKAP-2 polynucleotide is expressed; (b) incubating the sample in the presence of a reagent; (c) isolating polyadenylated RNA from the sample; (d) incubating the RNA with a polynucleotide probe specific for MAPKAP-2 kinase; (e) determining the amount of the probe hybridized to the RNA, where a level of expression of MAPKAP-2 is directly related to the amount of MAPKAP-2 probe hybridized to the RNA; and (f) comparing the effect of the reagent on MAPKAP-2 expression relative to a control, where a change in the expression indicates the presence of a reagent that modulates MAPKAP-2 expression. Treating (M18) a subject having a disorder associated with aberrant MAPKAP-2 kinase or nucleic acid expression or activity, comprises administering an agent which is a MAPKAP -2 modulator to the subject. The MAPKAP-2 modulator is a MAPKAP-2 kinase, MAPKAP-2 nucleic acid molecule, a peptide, a peptidomimetic, or other small molecule. The disorder is an immune-related disorder.

ACTIVITY - Immunomodulator; Antiinflammatory; Cytostatic; Antiarthritic. No biological data given.

MECHANISM OF ACTION - Gene therapy; Serine-Threonine-Kinase.

USE - (I) encodes (II) which may be used to treat an immune-related disorder (claimed). (I) is especially useful in regulating signal transduction in a cell, and in diagnosing or treating MAPKAP-2-mediated disorders, e.g. cell proliferative disorders, immune system disorders, inflammation, arthritis. The nucleic acid and the polypeptide may also be used in screening assays, predictive medicine, diagnostic or prognostic assays, chromosome mapping, tissue typing, pharmacogenomics and in monitoring clinical trials.

ADMINISTRATION - Administration is oral, topical or parenteral (e.g. intraarterial, intramuscular, subcutaneous, intramedullary, intrathecal, intraventricular, intravenous, intraperitoneal, or intranasal). The dosage is 0.001-50 mg/kg, preferably 0.1-1.0 mg/kg.

EXAMPLE - No relevant example given.(150 pages)

L9 ANSWER 14 OF 19 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2001306415 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11383510
TITLE: Heat shock protein 27 is a substrate of cGMP-dependent protein kinase in intact human platelets: phosphorylation-induced actin polymerization caused by HSP27 mutants.
AUTHOR: Butt E; Immler D; Meyer H E; Kotlyarov A; Laass K; Gaestel

M
CORPORATE SOURCE: Institute of Clinical Biochemistry and Pathochemistry, Medical University Clinic, Wurzburg, Germany.. butt@klin-biochem.uni-wuerzburg.de
SOURCE: The Journal of biological chemistry, (2001 Mar 9) Vol. 276, No. 10, pp. 7108-13.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 23 Jul 2001
Last Updated on STN: 20 Apr 2002
Entered Medline: 19 Jul 2001

AB Phosphorylation of heat shock protein 27 (Hsp27) in human platelets by mitogen-activated protein kinase-activated protein kinase (MAPKAP) 2 is associated with signaling events involved in platelet aggregation and regulation of microfilament organization. We now show that Hsp27 is also phosphorylated by cGMP-dependent protein kinase (cGK), a signaling system important for the inhibition of platelet aggregation. Stimulation of washed platelets with 8-para-chlorophenylthio-cGMP, a cGK specific activator, resulted in a time-dependent phosphorylation of Hsp27. This is supported by the ability of cGK to phosphorylate Hsp27 in vitro to an extent comparable with the cGK-mediated phosphorylation of its established substrate vasodilator-stimulated phosphoprotein. Studies with Hsp27 mutants identified threonine 143 as a yet uncharacterized phosphorylation site in Hsp27 specifically targeted by cGK. To test the hypothesis that cGK could inhibit platelet aggregation by phosphorylating Hsp27 and interfering with the MAPKAP kinase phosphorylation of Hsp27, the known MAPKAP kinase 2-phosphorylation sites (Ser15, Ser78, and Ser82) as well as Thr143 were replaced by negatively charged amino acids, which are considered to mimic phosphate groups, and tested in actin polymerization experiments. Mimicry at the MAPKAP kinase 2 phosphorylation sites led to mutants with a stimulating effect on actin polymerization. Mutation of the cGK-specific site Thr143 alone had no effect on actin polymerization, but in the MAPKAP kinase 2 phosphorylation-mimicking mutant, this mutation reduced the stimulation of actin polymerization significantly. These data suggest that phosphorylation of Hsp27 and Hsp27-dependent regulation of actin microfilaments contribute to the inhibitory effects of cGK on platelet function.

L9 ANSWER 15 OF 19 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:20610 BIOSIS
DOCUMENT NUMBER: PREV200100020610
TITLE: Two forms of MAPKAP kinase-2 are present in adult rat ventricular myocytes.
AUTHOR(S): Allen, B. G. [Reprint author]; Chevalier, D. [Reprint author]
CORPORATE SOURCE: Montreal, PQ, Canada
SOURCE: Canadian Journal of Cardiology, (September, 2000) Vol. 16, No. Supplement F, pp. 114F. print.
Meeting Info.: 53rd Annual Meeting of the Canadian Cardiovascular Society. Vancouver, British Columbia, Canada. October 20-November 01, 2000. Canadian Cardiovascular Society.
CODEN: CJCAEX. ISSN: 0828-282X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 3 Jan 2001
Last Updated on STN: 15 Feb 2002

L9 ANSWER 16 OF 19 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:470402 HCAPLUS
DOCUMENT NUMBER: 136:83416
TITLE: Signal transduction in the adapted heart: Implication of protein kinase C-dependent and -independent pathways
AUTHOR(S): Debarros, John; Das, Dipak K.
CORPORATE SOURCE: Department of Surgery, University of Connecticut School of Medicine, Farmington, CT, 06032, USA
SOURCE: Progress in Experimental Cardiology (2000), 3(Hypertrophied Heart), 3-16
CODEN: PEXCFF; ISSN: 1389-1774
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Cardioprotection as a result of myocardial adaptation to cellular stress is a product of evolution. Myocardial adaptation potentiates intracellular signaling involving diverse signal transduction pathways. Ischemic preconditioning, a specific form of myocardial adaptive response, occurs through both G proteins and receptor tyrosine kinase. Such preconditioning, mediated by cyclic episodes of brief reversible ischemia each followed by another brief period of reperfusion, leads to improvement in infarct size and ventricular recovery. Adaptation can also be achieved through other environmental stresses, including oxidative stress. Several triggers for signal transduction have been identified, including catecholamines, bradykinin, and adenosine. The processing of stress signals from signal initiation to propagation to eventual termination is the focus of this chapter. Signal initiation occurs through G-protein as well as receptor tyrosine kinase activation. Complex signaling processes involving MAP kinases, MAPKAP kinase 2, and protein kinase C have become central to our understanding of signal propagation. Signal termination resulting in biol. expression of signal propagation by means of gene expression and transcription regulation is the ultimate outcome of cellular stress response. This chapter especially examines these complex signal transduction processes that lead to the stress response and eventual adaptation, focusing primarily upon protein kinase C-dependent and -independent pathways.
REFERENCE COUNT: 92 THERE ARE 92 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 17 OF 19 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 1995:72710 SCISEARCH
THE GENUINE ARTICLE: QB851
TITLE: CHARACTERIZATION OF 45-KDA 54-KDA HSP27 KINASE, A STRESS-SENSITIVE KINASE WHICH MAY ACTIVATE THE PHOSPHORYLATION-DEPENDENT PROTECTIVE FUNCTION OF MAMMALIAN 27-KDA HEAT-SHOCK PROTEIN HSP27
AUTHOR: HUOT J (Reprint); LAMBERT H; LAVOIE J N; GUIMOND A; HOULE F; LANDRY J
CORPORATE SOURCE: UNIV LAVAL, HOTEL DIEU, CTR RECH CANCEROL, QUEBEC CITY, PQ G1R 2J6, CANADA
COUNTRY OF AUTHOR: CANADA
SOURCE: EUROPEAN JOURNAL OF BIOCHEMISTRY, (15 JAN 1995) Vol. 227, No. 1-2, pp. 416-427.
ISSN: 0014-2956.
PUBLISHER: SPRINGER VERLAG, 175 FIFTH AVE, NEW YORK, NY 10010.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 66
ENTRY DATE: Entered STN: 1995
Last Updated on STN: 1995
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Heat-shock protein 27 (HSP27) is a major target of phosphorylation upon cell stimulation with a variety of agents and has been suggested to have a phosphorylation-regulated function at the level of actin filaments. Here we investigated comparatively the mechanisms of HSP27 phosphorylation by oxidative stresses, exposures to tumor necrosis factor (TNF), heat shock and growth factors. Extracts of Chinese hamster or human cells exposed to H2O2, xanthine/xanthine oxidase, menadione or TNF contained up to 15-fold more HSP27 kinase activity than comparable extracts obtained from control cells. Induction of HSP27 kinase activity by TNF or H2O2 was completely inhibited by first treating the cells with the antioxidant N-acetyl-L-cysteine, suggesting that generation of reactive oxygen metabolites was the key triggering element of this induction. In contrast, prior treatment with acetylcysteine had no or little effect on the induction by thrombin, serum and heat shock. The kinase activity in extracts of cells stimulated by heat shock, H2O2, sodium arsenite, TNF or growth factors was identified by in-gel renaturation and purified approximate to 8000-fold by sequential chromatography. In all cases, the induced kinase activity was entirely associated with two polypeptides of 45 kDa and 54 kDa, identified as mitogen-activated-protein kinase-activated protein (MAPKAP) kinase-2 based on its reactivation in vitro by 42/44-kDa MAP kinases, its antigenic properties and its substrate specificity. The 45/54-kDa HSP27 kinase may play an important role in the cell response to oxidative stress. Overexpression of the wild-type HSP27 but not of a nonphosphorylatable form of human HSP27 in Chinese hamster cells conferred resistance to actin fragmentation by oxidative stress generated by H2O2. It is concluded that activation of the 45/54-kDa HSP27 kinase is a common mechanism of HSP27 phosphorylation to which converge both oxyradical-dependent and oxyradical-independent pathways and which may participate in a homeostatic response to stress at the level of actin microfilament.

L9 ANSWER 18 OF 19 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1993:596625 HCAPLUS
DOCUMENT NUMBER: 119:196625
TITLE: Epidermal growth factor and insulin stimulate MAP kinase activity in cultured hepatocytes
AUTHOR(S): Peak, Matthew; Yeaman, Stephen J.; Agius, Loranne
CORPORATE SOURCE: Dep. Med., Medical Sch., Newcastle upon Tyne, NE2 4HH, UK
SOURCE: Biochemical Society Transactions (1993), 21(4), 494S
CODEN: BCSTB5; ISSN: 0300-5127
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In this study the authors investigated the possible role of mitogen-activated protein kinase (MAPK) in the regulation of glycogen synthesis in rat hepatocyte cultures. MAPK activity was determined in hepatocyte cultures exposes to EGF, which inhibits glycogenesis and is a potent mitogen, and insulin, which stimulates glucogenesis and is not a mitogen. In control hepatocyte cultures two small peaks of myelin basic protein (MBP) phosphorylation activity were consistently observed These two peaks may represent the 42 and 44 kDa isoforms of MAPK demonstrated in rat liver exts. Treatment of hepatocytes with 100 nM insulin for 5 min stimulated the activity of peak 1 approx. 5-fold, but had no effect on the activity of peak 2. Similarly, in treatment with EGF for 5 min increased the MBP phosphorylating activity of peak 1 approx. 10-fold, while the activity of peak 2 was unaffected. These results demonstrate for the first time that both insulin and EGF rapidly activate MAPK activity in cultured hepatocytes from rat. The activation of MAPK by insulin is consistent with a previous study in which the activity of the 42 kDa MAPK isoform increased 4-fold within 4.5 min in the liver of rats injected with insulin. MAPK has been implicated in the mechanism of activation of glycogen synthesis by insulin. However, activation of MAPK may not be exclusively associated with stimulation of glycogen synthesis, since EGF, which inhibits glycogen synthesis in hepatocyte cultures, also activates

MAPK. The effect of EGF and insulin on glycogen synthesis may be determined by kinases downstream of MAPK in the signalling pathway. Thus, insulin may activate S6 kinase II and stimulate glycogenesis, whereas EGF may stimulate MAPKAP-2 and inhibit glycogen synthesis.

L9 ANSWER 19 OF 19 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1994:157417 HCAPLUS
DOCUMENT NUMBER: 120:157417
TITLE: The MAP kinase-activated protein kinase 2 contains a proline-rich SH3-binding domain
AUTHOR(S): Engel, Katrin; Plath, Kathrin; Gaestel, Matthias
CORPORATE SOURCE: Max-Delbrueck-Center of Molecular Medicine, R.-Roessle-Str.10, D-13122, Berlin, Germany
SOURCE: FEBS Letters (1993), 336(1), 143-7
CODEN: FEBLAL; ISSN: 0014-5793
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The protein sequence of MAP kinase-activated protein kinase 2 (MAPKAP kinase 2) deduced from mouse cDNA sequence reveals structural features of the enzyme, which could be of importance for its function: a proline-rich SH3-binding domain N-terminal to the catalytic region, a MAP kinase phosphorylation site and a bipartite nuclear targeting sequence located C-terminal to the catalytic region. The catalytic domain itself has the strongest homol. to calcium/calmodulin-dependent protein kinase II. Northern blot anal. demonstrates a 3.5 kb MAPKAP kinase 2 transcript which is ubiquitously expressed and, hence, co-expressed with the mRNA of the recently identified substrate Hsp25 in all tissues analyzed. However, the functional consequences of the nuclear targeting sequence present in MAPKAP kinase 2 suggest the existence of further substrates for the enzyme in the nucleus.

=> d his

(FILE 'HOME' ENTERED AT 16:11:16 ON 13 JUL 2006)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 16:11:42 ON 13 JUL 2006
L1 149956 S MITOGEN (W)ACTIVATED (3W) KINASE##
L2 37 S MAPKAP-2
L3 149966 S L1 OR L2
L4 7784549 S CLON? OR EXPRESS? OR RECOMBINANT
L5 85357 S L3 AND L4
L6 41653 S HUMAN AND L5
L7 5 S L2 (W)KINASE?
L8 4 DUP REM L7 (1 DUPLICATE REMOVED)
L9 19 DUP REM L2 (18 DUPLICATES REMOVED)

=> s (modulat? or inhibit? ot activat?)and l6
<------User Break------>

=> s (modulat? or inhibit? or activat?)and l6
L10 41652 (MODULAT? OR INHIBIT? OR ACTIVAT?) AND L6

=> s l2 and l10
L11 17 L2 AND L10

=> dup rem l11
PROCESSING COMPLETED FOR L11
L12 8 DUP REM L11 (9 DUPLICATES REMOVED)

=> d 1-8 ibib ab

L12 ANSWER 1 OF 8 MEDLINE on STN DUPLICATE 1

ACCESSION NUMBER: 2006074832 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16447221
TITLE: Activation of p38 MAPK is a key step in tumor necrosis factor-mediated inflammatory bone destruction.
AUTHOR: Zwerina Jochen; Hayer Silvia; Redlich Kurt; Bobacz Klaus; Kollias Giorgos; Smolen Josef S; Schett Georg
CORPORATE SOURCE: Medical University of Vienna, Vienna, Austria.
SOURCE: Arthritis and rheumatism, (2006 Feb) Vol. 54, No. 2, pp. 463-72.
Journal code: 0370605. ISSN: 0004-3591.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200603
ENTRY DATE: Entered STN: 8 Feb 2006
Last Updated on STN: 18 Mar 2006
Entered Medline: 17 Mar 2006

AB OBJECTIVE: To investigate whether activation of p38 MAPK is a crucial signaling factor in inflammatory bone destruction mediated by tumor necrosis factor (TNF). Mice overexpressing TNF were treated with 2 different inhibitors of p38 MAPK, and the effect of this treatment on joint inflammation and structural damage was assessed. METHODS: Human TNF-transgenic mice received systemic treatment with 2 different p38 MAPK inhibitors (RO4399247 and AVE8677). Treatment was started at the time of symptom onset and lasted for 6 weeks. Mice were assessed for clinical signs of arthritis, bone erosion, and cartilage damage. In addition, the effect of these inhibitors on osteoclast generation in vitro and in vivo was assessed. RESULTS: Both p38 MAPK inhibitors significantly reduced clinical signs of TNF-mediated arthritis. This was attributable to reducing synovial inflammation by 50% without affecting the cellular composition of the infiltrate. Synovial expression of interleukin-1 and RANKL was reduced upon p38 MAPK blockade, and activation of the molecular target MAPK-activated protein kinase 2 (MAPKAP-2) was also inhibited. Proteoglycan loss of articular cartilage was reduced by 50%, although p38 MAPK inhibition did not change matrix molecule synthesis by cultivated chondrocytes. Importantly, bone loss was almost completely prevented by p38 MAPK inhibition. The numbers of synovial osteoclasts and precursors were dramatically reduced, and both p38 MAPK inhibitors also inhibited in vitro osteoclastogenesis at micromolar concentrations and blocked activation of MAPKAP-2 as well as differentiation markers in cultured osteoclast precursors. CONCLUSION: These results suggest the major importance of p38 MAPK for TNF-mediated inflammatory bone destruction in arthritis and suggest that inhibition of p38 MAPK might be an important tool for reducing structural damage in rheumatoid arthritis.

L12 ANSWER 2 OF 8 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2006:2430 BIOSIS
DOCUMENT NUMBER: PREV200600001220
TITLE: P38 inhibition ameliorates TNF-mediated arthritis.
AUTHOR(S): Zwerina, J. [Reprint Author]; Hayer, S.; Redlich, K.; Smolen, J.; Schett, G.
CORPORATE SOURCE: Med Univ Vienna, Dept Internal Med 3, Div Rheumatol, Vienna, Austria
SOURCE: Annals of the Rheumatic Diseases, (JUL 2005) Vol. 64, No. Suppl. 3, pp. 170-171.
Meeting Info.: Annual European Congress of Rheumatology. Vienna, AUSTRIA. June 08 -11, 2005.
CODEN: ARDIAO. ISSN: 0003-4967.
DOCUMENT TYPE: Conference; (Meeting)

Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 14 Dec 2005
Last Updated on STN: 14 Dec 2005

L12 ANSWER 3 OF 8 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2006:5597 BIOSIS
DOCUMENT NUMBER: PREV200600003110
TITLE: Activation of p38MAPK is a key step in TNF-Mediated inflammatory bone destruction.
AUTHOR(S): Zwerina, Jochen [Reprint Author]; Hayer, Silvia; Redlich, Kurt; Bobacz, Klaus; Smolen, Josef S.; Schett, Georg
CORPORATE SOURCE: Med Univ Vienna, Vienna, Austria
SOURCE: Arthritis & Rheumatism, (SEP 2005) Vol. 52, No. 9, Suppl. S, pp. S160.
Meeting Info.: 69th Annual Scientific Meeting of the American-College-of-Rheumatology/40th Annual Scientific Meeting of the Association-of-Rheumatology-Health-Professionals. San Diego, CA, USA. November 12 -17, 2005. Amer Coll Rheumatol; Assoc Rheumatol Hlth Profess.
CODEN: ARHEAW. ISSN: 0004-3591.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 14 Dec 2005
Last Updated on STN: 14 Dec 2005

L12 ANSWER 4 OF 8 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2004462719 EMBASE
TITLE: MAP kinases and cell migration.
AUTHOR: Huang C.; Jacobson K.; Schaller M.D.
CORPORATE SOURCE: M.D. Schaller, Dept. of Cell/Developmental Biology, University of North Carolina, Chapel Hill, NC 27599-7090, United States. crispy4@med.unc.edu
SOURCE: Journal of Cell Science, (15 Sep 2004) Vol. 117, No. 20, pp. 4619-4628. .
Refs: 131
ISSN: 0021-9533 CODEN: JNCSAI
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 19 Nov 2004
Last Updated on STN: 19 Nov 2004
AB Recent studies have demonstrated that mitogen-activated protein kinases (MAPKs), including Jun N-terminus kinase (JNK), p38 and Erk, play crucial roles in cell migration. JNK, for example, regulates cell migration by phosphorylating paxillin, DCX, Jun and microtubule-associated proteins. Studies of p38 show that this MAPK modulates migration by phosphorylating MAPK-activated protein kinase 2/3 (MAPKAP 2/3), which appears to be important for directionality of migration. Erk governs cell movement by phosphorylating myosin light chain kinase (MLCK), calpain or FAK. Thus, the different kinases in the MAPK family all seem able to regulate cell migration but by distinct mechanisms.

L12 ANSWER 5 OF 8 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2004013081 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14694199
TITLE: Differentiation stage-specific activation of p38 mitogen-activated protein kinase isoforms in primary human erythroid cells.

AUTHOR: Uddin Shahab; Ah-Kang Jeong; Ulaszek Jodie; Mahmud Dolores; Wickrema Amittha
CORPORATE SOURCE: Section of Hematology/Oncology, University of Chicago, Chicago, IL 60637, USA.
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (2004 Jan 6) Vol. 101, No. 1, pp. 147-52. Electronic Publication: 2003-12-23. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200402
ENTRY DATE: Entered STN: 8 Jan 2004
Last Updated on STN: 2 Mar 2004
Entered Medline: 25 Feb 2004

AB p38alpha, p38beta, p38gamma, and p38delta are four isoforms of p38 mitogen-activated protein (MAP) kinase (MAPK) involved in multiple cellular functions such as cell proliferation, differentiation, apoptosis, and inflammation response. In the present study, we examined the mRNA expression pattern of each of the four isoforms during erythroid differentiation of primary erythroid progenitors. We show that p38alpha and p38gamma transcripts are expressed in early hematopoietic progenitors as well as in late differentiating erythroblasts, whereas p38delta mRNA is only expressed and active during the terminal phase of erythroid differentiation. On the other hand, p38beta is minimally expressed in early CD34(+) hematopoietic progenitors but not expressed in lineage-committed erythroid progenitors. We also determined the phosphorylation/activation of p38alpha, MAPK kinase 3/6, and MAPKAP-2 in response to erythropoietin and stem cell factor. We found that phosphorylation of p38alpha, MAPK kinase kinase 3/6 and MAPKAP-2 occurs only upon growth factor withdrawal in primary erythroid progenitors. Moreover, our data indicate that activation of p38alpha does not induce apoptosis or promote proliferation of erythroid progenitors. On the other hand, under steady-state culture conditions, both p38alpha and p38delta isoforms are increasingly phosphorylated activated in the terminal phase of differentiation. This increased phosphorylation/activity was accompanied by up-regulation of heat shock protein 27 phosphorylation. Finally, we demonstrate that tumor necrosis factor alpha, an inflammatory cytokine that is modulated by p38alpha, is expressed by differentiating erythroblasts and inhibition of p38alpha or tumor necrosis factor alpha results in reduction in differentiation. Taken together, our data demonstrate that both p38alpha and delta isoforms function to promote the late-stage differentiation of primary erythroid progenitors and are likely to be involved in functions related to erythrocyte membrane remodeling and enucleation.

L12 ANSWER 6 OF 8 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:180903 BIOSIS
DOCUMENT NUMBER: PREV200400180952
TITLE: Quantitative proteomic and genomic analysis of p38 MAPK signaling in transformed follicular lymphoma cells.
AUTHOR(S): Lin, Zhaosheng [Reprint Author]; Crockett, David K. [Reprint Author]; Jenson, Stephen D.; Lim, Megan S. [Reprint Author]; Elenitoba-Johnson, Kojo S. J. [Reprint Author]
CORPORATE SOURCE: Molecular Hematopathology, ARUP Institute for Clinical and Experimental Pathology, Salt Lake City, UT, USA
SOURCE: Blood, (November 16 2003) Vol. 102, No. 11, pp. 24a-25a. print.
Meeting Info.: 45th Annual Meeting of the American Society of Hematology. San Diego, CA, USA. December 06-09, 2003.

American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 7 Apr 2004
Last Updated on STN: 7 Apr 2004

AB The p38 mitogen-activated protein kinase (p38 MAPK) is a key mediator of extracellular growth factor and cytokine induced signaling pathways and has been implicated in the development of some human cancers. Our previous work showed evidence for p38 MAPK activation in a subset of transformed follicular lymphomas (Elenitoba-Johnson, et al. PNAS 2003; 100;7259). We further demonstrated that inhibition of p38 MAPK, using the pyridinyl imidazole inhibitor SB203580 resulted in dose- and time-dependent caspase 3-mediated apoptosis. In order to further elucidate the role of p38 MAPK in follicular lymphoma transformation, we have employed a systems biologic approach involving transcriptional profiling and quantitative proteomic analysis of transformed follicular lymphoma derived-cells (OCI-Ly1) treated with SB203580. Cultured OCI-Ly1 cells expressing native and phosphorylated-p38 MAPK were exposed to SB203580, and significant growth inhibition was achieved after 3 hours as determined by in vitro MTT (3-(4,5-dimethyl thiazol-2-yl)-2,5-diphenyl tetrazolium bromide) assays. Direct comparison of the transcriptomes of treated versus untreated cells at 3 and 21 hours was performed using a cDNA array format containing 9600 genes. Quantitative proteomic analysis was performed using cleavable isotope-coded affinity tags (ICATTM) and three-dimensional (strong cationic exchange, affinity and reverse-phase) chromatographic separation followed by tandem mass spectrometry. Gene expression profiling revealed differential expression (ltoreqor gtoreq1.5-fold) of 386 genes and ESTs in cells treated for 3 hours, and 532 genes and ESTs in cells treated for 21 hours. Majority of these genes and ESTs (52% for 3 hours and 91% for 21 hours) were downregulated in response to p38 MAPK inhibition, including genes encoding growth cytokines, transcriptional regulators and cytoskeletal proteins. Quantitative proteomic analysis unequivocally identified (XCorr values gtoreq2.0 for all cysteine containing peptides with DCn gtoreq0.1) 277 differentially expressed proteins at 3 hours and 350 proteins at 21 hours of treatment with SB203580., Consistent with the results of microarray analysis, 82% of the differentially expressed proteins were down-regulated at 3 hours and 76% at 21 hours. Analysis of functional groups of the differentially expressed proteins implicated components of diverse overlapping pathways including the IL-6/PI-3K, IGF-2/Ras/Raf, WNT8d/Frizzled, MAPKAP-2 and NFk B in p38 MAPK signaling. Our studies reveal the global cellular ramifications of p38 MAPK-mediated cellular signaling and its potential role in the pathogenesis of follicular lymphoma transformation. Furthermore, our results demonstrate the complementary nature of genomic and proteomic approaches in the evaluation of signal transduction pathways.

L12 ANSWER 7 OF 8 BIOTECHDS COPYRIGHT 2006 THE THOMSON CORP. on STN
ACCESSION NUMBER: 2003-08555 BIOTECHDS
TITLE: New isolated nucleic acid molecule encoding a human mitogen-activated protein kinase activating protein kinase-2 (MAPKAP-2), useful for treating immune-system related disorders, inflammation and arthritis; recombinant enzyme protein production and sense and antisense sequence for use in gene therapy
AUTHOR: LOGRASSO P; HAWKINS J; LISNOCK J M
PATENT ASSIGNEE: MERCK and CO INC
PATENT INFO: WO 2002090524 14 Nov 2002
APPLICATION INFO: WO 2002-US5670 25 Feb 2002

PRIORITY INFO: US 2001-272260 28 Feb 2001; US 2001-272260 28 Feb 2001
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2003-111970 [10]

AB DERWENT ABSTRACT:
NOVELTY - An isolated nucleic acid molecule (I) comprising a sequence of nucleotides that encode a human mitogen-activated protein kinase activating protein kinase-2 (MAPKAP-2 kinase), and a coding region that encodes a splice variant of a MAPKAP-2 kinase, is new.

DETAILED DESCRIPTION - The nucleotide is selected from sequences that: (a) Encode a human MAPKAP-2 kinase and comprise a sequence of 1191 (S1) or 1203 (S2) bp given in the specification; (b) Encode a human MAPKAP-2 kinase and hybridize under conditions of high stringency to the complement of S1 or S2, and, if it is DNA, is fully complementary, or if its is RNA, is identical to mRNA native to a human cell; (c) Degenerate with the MAPKAP-2 polypeptide and encode sequence of (a) or (b); and (d) Encode a sequence having 396 (S3) or 400 (S4) amino acids given in the specification. INDEPENDENT CLAIMS are also included for the following: (1) A polypeptide (II) comprising (S3), or a variant at least 80% identical to (S3) and differs from (S3) only in one or more amino acid substitutions, additions of terminal amino acid residues and/or deletions of terminal amino acid residues, where the ability to phosphorylate Hsp-27 is not diminished; (2) Host cells (III) transfected or transformed with (I), where the cells are bacterial cells, mammalian cells or amphibian oocytes and the nucleic acid molecule is heterologous to the cells; (3) Detecting (M1) MAPKAP-2 messenger RNA in a biological sample; (4) Identifying (M2) DNA sequences encoding a MAPKAP-2 kinase; (5) Identifying (M3) MAPKAP-2 kinase in a sample; (6) Bioassay (M4) for identifying a compound or reagent which modulates activity of human MAPKAP-2 kinase; (7) Monitoring (M5) the effectiveness of a treatment with a test compound for MAPKAP -2-mediated disease state; (8) Determining (M6) regression, progression or onset of a disease state manifested by a dysfunctional signal transducing MAPKAP-2 kinase;(9) Screening (M7) test compounds for use as inflammation inhibitors;(10) Monitoring (M8) the efficacy of an agent in correcting an abnormal level of the above polypeptide in a prone subject; (11) Identifying (M9) ligand(s) that activate a MAPKAP-2 kinase; (12) An antibody specific for the gene product of (I); (13) A recombinant non-human cell line that has been engineered to express a heterologous protein, comprising (III); (14) An expression vector comprising (I) operably linked to a regulatory nucleotide sequence that controls the expression of the nucleic acid molecule; (15) Detecting (M10) a binding partner for a MAPKAP-2 kinase in a sample suspected of having the binding partner; (16) Identifying (M11) a compound which modulates the binding or kinase activity of a kinase polypeptide having S2; (17) Modulating (M12) endogenous signal transducing activity of the MAPKAP-2 kinase in a mammal; (18) Identifying (M13) a compound which modulates the binding or kinase activity of a naturally-occurring allelic variant of the polypeptide in (S3); (19) Phosphorylating (M14) a serine-containing substrate; (20) Identifying (M15) a reagent that modulates MAPKAP-2 activity; (21) Identifying (M16) a reagent that modulates MAPKAP-2 synthesis; (22) Identifying (M17) a reagent that modulates MAPKAP-2 expression; (23) Treating (M18) a subject having a disorder associated with aberrant MAPKAP-2 kinase or nucleic acid expression or activity; and (24) Kits for detecting MAPKAP-2 or the nucleic acid molecule,

comprising: (a) a buffer and a labeled antibody which specifically binds to a MAPKAP-2 kinase having serine, threonine, and tyrosine kinase activity, where the sample to be tested is mixed with the buffer and the antibody; or (b) a buffer and a nucleic acid molecule comprising at least about 20 nucleotides capable of hybridizing to a nucleic acid sequence encoding MAPKAP-2 or its complement under stringent hybridization conditions, and instructions for use.

BIOTECHNOLOGY - Preparation: The nucleic acid was prepared using standard isolation techniques. Preferred Nucleic Acid: The isolated nucleic acid molecule is cDNA. The nucleic acid molecule may also comprise a nucleotide sequence encoding a polypeptide that has at least 80% identity to S3, where the 80% identity defines the amino acid alterations allowed for S3 which are determined by the equation: Na = Xa-(XaY); Na = maximum number of amino acid alterations; Xa = total number of amino acids in S3; and Y = a value of 0.80 Any non-integer product of Xa and Y is rounded down to the nearest integer prior to subtracting the product from Xa. The nucleic acid molecule has a sequence that is at least 80% identical to a nucleotide sequence encoding the above polypeptide. Preferred Polypeptide: (II) is a human MAPKAP-2 kinase encoded by (I) or a splice variant that encodes a MAPKAP-2 kinase comprising (S3) or by a nucleotide acid molecule comprising a sequence that hybridizes to the complement of (S1). Preferred Method: (M1) comprises introducing (I) into a host cell suspected of expressing a MAPKAP-2 kinase to form a complex, and detecting the presence of the complex. In (M2), identifying DNA sequences encoding a MAPKAP-2 kinase comprises probing a cDNA library or a genomic library with a labeled probe, and recovering from the library those sequences having a significant degree of homology relative to the probe, where the probe comprises (I). (M3) comprises introducing (I) into eukaryotic cells, and detecting second messenger activity in the cells, where the activity is mediated by a polypeptide encoded by (I). The bioassay (M4) for identifying a test compound which modulates the activity of a human MAPKAP-2 kinase, comprises: (a) measuring the second messenger activity of eukaryotic cells transformed with the DNA encoding the kinase in the absence of the test compound to obtain a first measurement; (b) measuring the second messenger activity of the eukaryotic cells in the presence of the test compound to obtain a second measurement; and (c) comparing the first and second measurements and identifying those compounds that result in a difference between the 2 measurements as a test compound that modulates the activity of the MAPKAP-2 kinase, where the eukaryotic cells express a functional human parathyroid hormone-2 polypeptide. In (M5), monitoring comprises: (a) obtaining a pre-administration sample from a subject suspected of having a dysfunctional MAPKAP-2-mediated disease; (b) detecting a level of expression or activity of a MAPKAP-2 kinase-encoding mRNA or genomic DNA in the pre-administration sample to obtain a first measurement; (c) detecting a level of expression or activity of the MAPKAP-2 kinase-encoding mRNA or genomic DNA in a post-administration sample to obtain a second measurement; (d) comparing the level of expression or activity of the kinase in the first and second measurements; and (e) altering the administration of the compound to the subject accordingly. Determining (M6) regression, progression or onset of a disease state manifested by a dysfunctional signal transducing MAPKAP-2 kinase, comprises: (a) contacting a cDNA or mRNA containing sample from a subject suspected of suffering from the disease, with the nucleic acid hybridization probe under conditions favoring binding of the probe to the cDNA or mRNA to form a complex; and (b) detecting the complex as an indication that the subject is at risk of developing the disease state. Alternatively, (M6) comprises contacting a sample from a patient with the disorder with a detectable probe that is

specific for the gene product of (I), where formation of the probe/gene product complex indicates regression, progression or onset of the pathological disorder in the patient. The probe is an antibody labeled with a radioactive label or an enzyme. (M7) comprises contacting a test compound with a MAPKAP-2 kinase encoded by (I), and testing the contacted kinase protein for its ability to bind or to phosphorylate Hsp-27, where a test compound that inhibits the binding of the MAPKAP-2 kinase protein to the Hsp-27 is a candidate drug for treating inflammation. In (M8), monitoring comprises administering the agent and determining the level of the polypeptide, where a change in the level of the polypeptide towards a normal level indicates the efficacy of the agent. Identifying (M9) ligand(s) that activate a MAPKAP-2 kinase, comprises: (a) contacting endogenous MAPKAP-2 kinase-deficient host cells with a candidate compound suspected of activating the kinase activity, where the host cells contain a reporter gene functionally linked to a transcriptional control element; and an exogenous gene encoding the kinase, where the transcriptional control element, upon activation, induces expression of the reporter gene(s); (b) monitoring induction of the reporter gene(s); and (c) identifying ligand(s) that activate the polypeptide. (M10) comprises contacting the sample with the MAPKAP-2 under conditions favoring binding of the kinase to the binding partner, and determining the presence of the binding partner in the sample by detecting the binding of the kinase to the binding partner. In (M11), identifying comprises contacting a cell expressing the polypeptide with a test compound under conditions suitable for modulation of the binding or kinase activity of the polypeptide, and detecting the modulation of the activity or the binding of the kinase polypeptide by the test compound. Preferably, the agent inhibits or stimulates MAPKAP-2 activity, or modulates the expression of MAPKAP-2 by modulating transcription of a MAPKAP-2 gene or translation of a MAPKAP-2 mRNA. The agent may be an antibody that specifically binds to the kinase, or a nucleic acid molecule having a sequence that is antisense to the coding strand of the MAPKAP-2 mRNA or gene. (M12) comprises contacting a cell capable of expressing MAPKAP-2 with the compound as in (M11).

Modulation of the activity of the polypeptide is detected by direct binding of the test compound to the polypeptide, or by using an assay for MAPKAP-2 kinase activity (based on the phosphorylation of a MAPKAP-2 substrate). Direct binding may be determined by lysing the cell, and performing an immunoprecipitation. In addition, the direct binding may be determined by a yeast 2-hybrid assay. In (M13), the allelic variant is encoded by the nucleic acid molecule which hybridizes to the complement of a nucleic acid molecule consisting of (S1) in 6 x SSC at 45 degrees C, followed by one or more washes in 0.2 x SSC, 0.1% SDS at 50-65 degrees C, and the method comprises: (a) contacting a cell expressing the allelic variant with a test compound under conditions that modulate the binding or kinase activity of the variant; and (b) detecting modulation of the binding or kinase activity of the allelic variant by the test compound. (M14) comprises: (a) incubating the substrate with a concentration of ATP and an enzyme having at least 84% homology to (S1); and (b) measuring the amount of phosphorylation of the substrate. The method further comprises forming a mixture of the enzyme and a candidate antagonist or agonist of the enzyme, and measuring the effect of the candidate antagonist or agonist on the amount of phosphorylation of the substrate. In (M15), identifying comprises: (a) obtaining a test sample containing the MAPKAP-2 kinase and a reagent; (b) incubating the test sample with MAPKAP-2 substrate and with labeled phosphate under conditions that allow phosphorylation of the substrate; (c) determining the rate of

incorporation of labeled phosphate into the substrate, where the rate of incorporation is a measure of MAPKAP-2 activity; and (d) comparing the effect of the reagent on MAPKAP-2 activity relative to a control, where a change in the activity indicates the presence of a reagent capable of modulating MAPKAP -2 activity. The MAPKAP-2 substrate is Hsp-25, Hsp-27 or ALT2. The modulation is inhibition of MAPKAP-2 activity. The reagent is an antisense oligonucleotide, a ribozyme, a tumor necrosis factor or an interleukin-1. (M16) comprises: (a) providing a test sample containing the MAPKAP-2 kinase; (b) incubating the sample in the presence of a reagent; (c) fractionating proteins present in the sample by gel electrophoresis; (d) transferring the proteins onto a membrane; (e) probing the proteins with a labeled antibody specific to the MAPKAP-2 kinase, where the level of the synthesis is determined by the amount of the antibody detected; and (f) comparing the effect of the reagent on MAPKAP-2 synthesis relative to a control, where a change in the synthesis indicates the presence of a reagent that modulates MAPKAP-2 synthesis.
(M17) comprises: (a) providing a test sample in which a MAPKAP-2 polynucleotide is expressed; (b) incubating the sample in the presence of a reagent; (c) isolating polyadenylated RNA from the sample; (d) incubating the RNA with a polynucleotide probe specific for MAPKAP-2 kinase; (e) determining the amount of the probe hybridized to the RNA, where a level of expression of MAPKAP-2 is directly related to the amount of MAPKAP-2 probe hybridized to the RNA; and (f) comparing the effect of the reagent on MAPKAP-2 expression relative to a control, where a change in the expression indicates the presence of a reagent that modulates MAPKAP-2 expression.
Treating (M18) a subject having a disorder associated with aberrant MAPKAP-2 kinase or nucleic acid expression or activity, comprises administering an agent which is a MAPKAP-2 modulator to the subject. The MAPKAP-2 modulator is a MAPKAP-2 kinase, MAPKAP-2 nucleic acid molecule, a peptide, a peptidomimetic, or other small molecule. The disorder is an immune-related disorder.

ACTIVITY - Immunomodulator; Antiinflammatory; Cytostatic; Antiarthritic. No biological data given.

MECHANISM OF ACTION - Gene therapy; Serine-Threonine-Kinase.

USE - (I) encodes (II) which may be used to treat an immune-related disorder (claimed). (I) is especially useful in regulating signal transduction in a cell, and in diagnosing or treating MAPKAP-2-mediated disorders, e.g. cell proliferative disorders, immune system disorders, inflammation, arthritis. The nucleic acid and the polypeptide may also be used in screening assays, predictive medicine, diagnostic or prognostic assays, chromosome mapping, tissue typing, pharmacogenomics and in monitoring clinical trials.

ADMINISTRATION - Administration is oral, topical or parenteral (e.g. intraarterial, intramuscular, subcutaneous, intramedullary, intrathecal, intraventricular, intravenous, intraperitoneal, or intranasal). The dosage is 0.001-50 mg/kg, preferably 0.1-1.0 mg/kg.

EXAMPLE - No relevant example given.(150 pages)

L12 ANSWER 8 OF 8 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:470402 HCAPLUS
DOCUMENT NUMBER: 136:83416
TITLE: Signal transduction in the adapted heart: Implication of protein kinase C-dependent and -independent pathways
AUTHOR(S): Debarros, John; Das, Dipak K.
CORPORATE SOURCE: Department of Surgery, University of Connecticut

School of Medicine, Farmington, CT, 06032, USA
SOURCE: Progress in Experimental Cardiology (2000), 3(Hypertrophied Heart), 3-16
CODEN: PEXCFF; ISSN: 1389-1774
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Cardioprotection as a result of myocardial adaptation to cellular stress is a product of evolution. Myocardial adaptation potentiates intracellular signaling involving diverse signal transduction pathways. Ischemic preconditioning, a specific form of myocardial adaptive response, occurs through both G proteins and receptor tyrosine kinase. Such preconditioning, mediated by cyclic episodes of brief reversible ischemia each followed by another brief period of reperfusion, leads to improvement in infarct size and ventricular recovery. Adaptation can also be achieved through other environmental stresses, including oxidative stress. Several triggers for signal transduction have been identified, including catecholamines, bradykinin, and adenosine. The processing of stress signals from signal initiation to propagation to eventual termination is the focus of this chapter. Signal initiation occurs through G-protein as well as receptor tyrosine kinase activation. Complex signaling processes involving MAP kinases, MAPKAP kinase 2, and protein kinase C have become central to our understanding of signal propagation. Signal termination resulting in biol. expression of signal propagation by means of gene expression and transcription regulation is the ultimate outcome of cellular stress response. This chapter especially examines these complex signal transduction processes that lead to the stress response and eventual adaptation, focusing primarily upon protein kinase C-dependent and -independent pathways.
REFERENCE COUNT: 92 THERE ARE 92 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
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L3        149966 S L1 OR L2
L4       7784549 S CLON? OR EXPRESS? OR RECOMBINANT
L5         85357 S L3 AND L4
L6         41653 S HUMAN AND L5
L7             5 S L2 (W)KINASE?
L8             4 DUP REM L7 (1 DUPLICATE REMOVED)
L9            19 DUP REM L2 (18 DUPLICATES REMOVED)
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L12            8 DUP REM L11 (9 DUPLICATES REMOVED)
                 E LOGRASSO P/AU
L13          175 S E3-E7
                 E HAWKINS J/AU
L14          540 S E3
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L17            2 L2 AND L16

=> d 1-2 ibib ab

L17   ANSWER 1 OF 2  BIOTECHDS COPYRIGHT 2006 THE THOMSON CORP. on STN
ACCESSION NUMBER: 2003-08555  BIOTECHDS
TITLE:            New isolated nucleic acid molecule encoding a human
                  mitogen-activated protein kinase activating protein kinase-2
                  (MAPKAP-2), useful for treating
                  immune-system related disorders, inflammation and arthritis;
                     recombinant enzyme protein production and sense and
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antisense sequence for use in gene therapy

AUTHOR: LOGRASSO P; HAWKINS J; LISNOCK J M

PATENT ASSIGNEE: MERCK and CO INC

PATENT INFO: WO 2002090524 14 Nov 2002

APPLICATION INFO: WO 2002-US5670 25 Feb 2002

PRIORITY INFO: US 2001-272260 28 Feb 2001; US 2001-272260 28 Feb 2001

DOCUMENT TYPE: Patent

LANGUAGE: English

OTHER SOURCE: WPI: 2003-111970 [10]

AB DERWENT ABSTRACT:

NOVELTY - An isolated nucleic acid molecule (I) comprising a sequence of nucleotides that encode a human mitogen-activated protein kinase activating protein kinase-2 (MAPKAP-2 kinase), and a coding region that encodes a splice variant of a MAPKAP-2 kinase, is new.

DETAILED DESCRIPTION - The nucleotide is selected from sequences that: (a) Encode a human MAPKAP-2 kinase and comprise a sequence of 1191 (S1) or 1203 (S2) bp given in the specification; (b) Encode a human MAPKAP-2 kinase and hybridize under conditions of high stringency to the complement of S1 or S2, and, if it is DNA, is fully complementary, or if its is RNA, is identical to mRNA native to a human cell; (c) Degenerate with the MAPKAP-2 polypeptide and encode sequence of (a) or (b); and (d) Encode a sequence having 396 (S3) or 400 (S4) amino acids given in the specification. INDEPENDENT CLAIMS are also included for the following: (1) A polypeptide (II) comprising (S3), or a variant at least 80% identical to (S3) and differs from (S3) only in one or more amino acid substitutions, additions of terminal amino acid residues and/or deletions of terminal amino acid residues, where the ability to phosphorylate Hsp-27 is not diminished; (2) Host cells (III) transfected or transformed with (I), where the cells are bacterial cells, mammalian cells or amphibian oocytes and the nucleic acid molecule is heterologous to the cells; (3) Detecting (M1) MAPKAP-2 messenger RNA in a biological sample; (4) Identifying (M2) DNA sequences encoding a MAPKAP-2 kinase; (5) Identifying (M3) MAPKAP-2 kinase in a sample; (6) Bioassay (M4) for identifying a compound or reagent which modulates activity of human MAPKAP-2 kinase; (7) Monitoring (M5) the effectiveness of a treatment with a test compound for MAPKAP-2-mediated disease state; (8) Determining (M6) regression, progression or onset of a disease state manifested by a dysfunctional signal transducing MAPKAP-2 kinase;(9) Screening (M7) test compounds for use as inflammation inhibitors;(10) Monitoring (M8) the efficacy of an agent in correcting an abnormal level of the above polypeptide in a prone subject; (11) Identifying (M9) ligand(s) that activate a MAPKAP-2 kinase; (12) An antibody specific for the gene product of (I); (13) A recombinant non-human cell line that has been engineered to express a heterologous protein, comprising (III); (14) An expression vector comprising (I) operably linked to a regulatory nucleotide sequence that controls the expression of the nucleic acid molecule; (15) Detecting (M10) a binding partner for a MAPKAP-2 kinase in a sample suspected of having the binding partner; (16) Identifying (M11) a compound which modulates the binding or kinase activity of a kinase polypeptide having S2; (17) Modulating (M12) endogenous signal transducing activity of the MAPKAP-2 kinase in a mammal; (18) Identifying (M13) a compound which modulates the binding or kinase activity of a naturally-occurring allelic variant of the polypeptide in (S3); (19) Phosphorylating (M14) a serine-containing substrate; (20) Identifying (M15) a reagent that modulates MAPKAP-2 activity; (21) Identifying (M16) a reagent that modulates MAPKAP-2 synthesis; (22) Identifying (M17) a reagent that modulates MAPKAP-2 expression; (23) Treating (M18) a subject having a disorder associated with aberrant MAPKAP

-2 kinase or nucleic acid expression or activity; and (24) Kits for detecting MAPKAP-2 or the nucleic acid molecule, comprising: (a) a buffer and a labeled antibody which specifically binds to a MAPKAP-2 kinase having serine, threonine, and tyrosine kinase activity, where the sample to be tested is mixed with the buffer and the antibody; or (b) a buffer and a nucleic acid molecule comprising at least about 20 nucleotides capable of hybridizing to a nucleic acid sequence encoding MAPKAP-2 or its complement under stringent hybridization conditions, and instructions for use.

BIOTECHNOLOGY - Preparation: The nucleic acid was prepared using standard isolation techniques. Preferred Nucleic Acid: The isolated nucleic acid molecule is cDNA. The nucleic acid molecule may also comprise a nucleotide sequence encoding a polypeptide that has at least 80% identity to S3, where the 80% identity defines the amino acid alterations allowed for S3 which are determined by the equation: Na = Xa-(XaY); Na = maximum number of amino acid alterations; Xa = total number of amino acids in S3; and Y = a value of 0.80 Any non-integer product of Xa and Y is rounded down to the nearest integer prior to subtracting the product from Xa. The nucleic acid molecule has a sequence that is at least 80% identical to a nucleotide sequence encoding the above polypeptide. Preferred Polypeptide: (II) is a human MAPKAP -2 kinase encoded by (I) or a splice variant that encodes a MAPKAP-2 kinase comprising (S3) or by a nucleotide acid molecule comprising a sequence that hybridizes to the complement of (S1). Preferred Method: (M1) comprises introducing (I) into a host cell suspected of expressing a MAPKAP-2 kinase to form a complex, and detecting the presence of the complex. In (M2), identifying DNA sequences encoding a MAPKAP-2 kinase comprises probing a cDNA library or a genomic library with a labeled probe, and recovering from the library those sequences having a significant degree of homology relative to the probe, where the probe comprises (I). (M3) comprises introducing (I) into eukaryotic cells, and detecting second messenger activity in the cells, where the activity is mediated by a polypeptide encoded by (I). The bioassay (M4) for identifying a test compound which modulates the activity of a human MAPKAP-2 kinase, comprises: (a) measuring the second messenger activity of eukaryotic cells transformed with the DNA encoding the kinase in the absence of the test compound to obtain a first measurement; (b) measuring the second messenger activity of the eukaryotic cells in the presence of the test compound to obtain a second measurement; and (c) comparing the first and second measurements and identifying those compounds that result in a difference between the 2 measurements as a test compound that modulates the activity of the MAPKAP-2 kinase, where the eukaryotic cells express a functional human parathyroid hormone-2 polypeptide. In (M5), monitoring comprises: (a) obtaining a pre-administration sample from a subject suspected of having a dysfunctional MAPKAP-2-mediated disease; (b) detecting a level of expression or activity of a MAPKAP-2 kinase-encoding mRNA or genomic DNA in the pre-administration sample to obtain a first measurement; (c) detecting a level of expression or activity of the MAPKAP-2 kinase-encoding mRNA or genomic DNA in a post-administration sample to obtain a second measurement; (d) comparing the level of expression or activity of the kinase in the first and second measurements; and (e) altering the administration of the compound to the subject accordingly. Determining (M6) regression, progression or onset of a disease state manifested by a dysfunctional signal transducing MAPKAP-2 kinase, comprises: (a) contacting a cDNA or mRNA containing sample from a subject suspected of suffering from the disease, with the nucleic acid hybridization probe under conditions favoring binding of the probe to the cDNA or mRNA to form a complex; and (b) detecting the complex as an indication that the subject is at risk of developing the disease state. Alternatively, (M6) comprises contacting a sample from a patient with the

disorder with a detectable probe that is specific for the gene product of (I), where formation of the probe/gene product complex indicates regression, progression or onset of the pathological disorder in the patient. The probe is an antibody labeled with a radioactive label or an enzyme. (M7) comprises contacting a test compound with a MAPKAP -2 kinase encoded by (I), and testing the contacted kinase protein for its ability to bind or to phosphorylate Hsp-27, where a test compound that inhibits the binding of the MAPKAP-2 kinase protein to the Hsp-27 is a candidate drug for treating inflammation. In (M8), monitoring comprises administering the agent and determining the level of the polypeptide, where a change in the level of the polypeptide towards a normal level indicates the efficacy of the agent. Identifying (M9) ligand(s) that activate a MAPKAP-2 kinase, comprises: (a) contacting endogenous MAPKAP-2 kinase-deficient host cells with a candidate compound suspected of activating the kinase activity, where the host cells contain a reporter gene functionally linked to a transcriptional control element; and an exogenous gene encoding the kinase, where the transcriptional control element, upon activation, induces expression of the reporter gene(s); (b) monitoring induction of the reporter gene(s); and (c) identifying ligand(s) that activate the polypeptide. (M10) comprises contacting the sample with the MAPKAP-2 under conditions favoring binding of the kinase to the binding partner, and determining the presence of the binding partner in the sample by detecting the binding of the kinase to the binding partner. In (M11), identifying comprises contacting a cell expressing the polypeptide with a test compound under conditions suitable for modulation of the binding or kinase activity of the polypeptide, and detecting the modulation of the activity or the binding of the kinase polypeptide by the test compound. Preferably, the agent inhibits or stimulates MAPKAP-2 activity, or modulates the expression of MAPKAP-2 by modulating transcription of a MAPKAP-2 gene or translation of a MAPKAP-2 mRNA. The agent may be an antibody that specifically binds to the kinase, or a nucleic acid molecule having a sequence that is antisense to the coding strand of the MAPKAP-2 mRNA or gene. (M12) comprises contacting a cell capable of expressing MAPKAP-2 with the compound as in (M11). Modulation of the activity of the polypeptide is detected by direct binding of the test compound to the polypeptide, or by using an assay for MAPKAP-2 kinase activity (based on the phosphorylation of a MAPKAP-2 substrate). Direct binding may be determined by lysing the cell, and performing an immunoprecipitation. In addition, the direct binding may be determined by a yeast 2-hybrid assay. In (M13), the allelic variant is encoded by the nucleic acid molecule which hybridizes to the complement of a nucleic acid molecule consisting of (S1) in 6 x SSC at 45 degrees C, followed by one or more washes in 0.2 x SSC, 0.1% SDS at 50-65 degrees C, and the method comprises: (a) contacting a cell expressing the allelic variant with a test compound under conditions that modulate the binding or kinase activity of the variant; and (b) detecting modulation of the binding or kinase activity of the allelic variant by the test compound. (M14) comprises: (a) incubating the substrate with a concentration of ATP and an enzyme having at least 84% homology to (S1); and (b) measuring the amount of phosphorylation of the substrate. The method further comprises forming a mixture of the enzyme and a candidate antagonist or agonist of the enzyme, and measuring the effect of the candidate antagonist or agonist on the amount of phosphorylation of the substrate. In (M15), identifying comprises: (a) obtaining a test sample containing the MAPKAP-2 kinase and a reagent; (b) incubating the test sample with MAPKAP-2 substrate and with labeled phosphate under conditions that allow phosphorylation of the substrate; (c) determining the rate of incorporation of labeled phosphate into the substrate, where the rate of incorporation is a measure of MAPKAP -2 activity; and (d) comparing the effect of the reagent on

MAPKAP-2 activity relative to a control, where a change in the activity indicates the presence of a reagent capable of modulating MAPKAP-2 activity. The MAPKAP-2 substrate is Hsp-25, Hsp-27 or ALT2. The modulation is inhibition of MAPKAP-2 activity. The reagent is an antisense oligonucleotide, a ribozyme, a tumor necrosis factor or an interleukin-1. (M16) comprises: (a) providing a test sample containing the MAPKAP-2 kinase; (b) incubating the sample in the presence of a reagent; (c) fractionating proteins present in the sample by gel electrophoresis; (d) transferring the proteins onto a membrane; (e) probing the proteins with a labeled antibody specific to the MAPKAP-2 kinase, where the level of the synthesis is determined by the amount of the antibody detected; and (f) comparing the effect of the reagent on MAPKAP-2 synthesis relative to a control, where a change in the synthesis indicates the presence of a reagent that modulates MAPKAP-2 synthesis. (M17) comprises: (a) providing a test sample in which a MAPKAP-2 polynucleotide is expressed; (b) incubating the sample in the presence of a reagent; (c) isolating polyadenylated RNA from the sample; (d) incubating the RNA with a polynucleotide probe specific for MAPKAP-2 kinase; (e) determining the amount of the probe hybridized to the RNA, where a level of expression of MAPKAP-2 is directly related to the amount of MAPKAP-2 probe hybridized to the RNA; and (f) comparing the effect of the reagent on MAPKAP-2 expression relative to a control, where a change in the expression indicates the presence of a reagent that modulates MAPKAP-2 expression. Treating (M18) a subject having a disorder associated with aberrant MAPKAP-2 kinase or nucleic acid expression or activity, comprises administering an agent which is a MAPKAP-2 modulator to the subject. The MAPKAP-2 modulator is a MAPKAP-2 kinase, MAPKAP-2 nucleic acid molecule, a peptide, a peptidomimetic, or other small molecule. The disorder is an immune-related disorder.

ACTIVITY - Immunomodulator; Antiinflammatory; Cytostatic; Antiarthritic. No biological data given.

MECHANISM OF ACTION - Gene therapy; Serine-Threonine-Kinase.

USE - (I) encodes (II) which may be used to treat an immune-related disorder (claimed). (I) is especially useful in regulating signal transduction in a cell, and in diagnosing or treating MAPKAP-2-mediated disorders, e.g. cell proliferative disorders, immune system disorders, inflammation, arthritis. The nucleic acid and the polypeptide may also be used in screening assays, predictive medicine, diagnostic or prognostic assays, chromosome mapping, tissue typing, pharmacogenomics and in monitoring clinical trials.

ADMINISTRATION - Administration is oral, topical or parenteral (e.g. intraarterial, intramuscular, subcutaneous, intramedullary, intrathecal, intraventricular, intravenous, intraperitoneal, or intranasal). The dosage is 0.001-50 mg/kg, preferably 0.1-1.0 mg/kg.

EXAMPLE - No relevant example given.(150 pages)

L17 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER:	2002:869065 HCAPLUS
DOCUMENT NUMBER:	137:364432
TITLE:	cDNA and protein sequences of human MAPKAP-2 kinases and their uses
INVENTOR(S):	Lograsso, Philip; Hawkins, Julio; Lisnock, Jean Marie
PATENT ASSIGNEE(S):	Merck & Co., Inc., USA
SOURCE:	PCT Int. Appl., 150 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2002090524	A2	20021114	WO 2002-US5670		20020225
WO 2002090524	A3	20030508			
W: CA, JP, US					
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR					
CA 2438978	AA	20021114	CA 2002-2438978		20020225
EP 1366146	A2	20031203	EP 2002-731100		20020225
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR					
JP 2004532035	T2	20041021	JP 2002-587586		20020225
US 2004170995	A1	20040902	US 2004-469221		20040211
PRIORITY APPLN. INFO.:			US 2001-272260P	P	20010228
			WO 2002-US5670	W	20020225

AB This invention provides cDNA and protein sequence of a novel human MAPKAP-2 kinase and its truncated isoform. The invention also provides the process of preparation of MAPKAP-2 by expressing in insect and mammalian cell lines. The MAPKAP-2 kinase can be used in drug screening, diagnosis and therapeutics.

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L5        85357 S L3 AND L4
L6        41653 S HUMAN AND L5
L7            5 S L2 (W)KINASE?
L8            4 DUP REM L7 (1 DUPLICATE REMOVED)
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L14         540 S E3
                E LISNOCK J M/AU
L15          25 S E3-E5
L16         716 S L13 OR L14 OR L15
L17           2 S L2 AND L16
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